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HISTOPATHOLOGY
OF THE SKIN



HISTOPATHOLOGY OF THE SKIN

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In Memory of My Father
DR. ALEXANDER LEVER
1877-1946

My First Teacher in Dermatology

Preface to the Second Edition

Descriptive histopathology is regarded by some as a static science in which nowadays but few concepts change. But this is not so. Many advances have been made in the field of dermatopathology in only the five years that have passed since the appearance of the First Edition of this book. Consequently, many changes were necessary for this Second Edition.

Important advances have been made in recent years in the histologic diagnosis of the vesicular and the bullous diseases, especially of pemphigus. Therefore, the descriptions of these diseases have been entirely rewritten and brought together into a new, separate chapter. Because of changes in the concept of the histogenesis of the nevus cell, the chapter on nevi and melanomas also has been rewritten. The use of the periodic acid-Schiff reaction for the demonstration of fungi in tissue is an important advance which is taken due notice of in the chapter on fungus diseases. Extensive changes also have been made, for instance, in the descriptions of kraurosis vulvae, the purpuras and verruca. Furthermore, discussion of the following diseases has been incorporated because recent work has increased the interest of dermatologists in them: beryllium granuloma, papular myxedema, porphyria, ochronosis, hibernoma and hemangiopericytoma. Many changes have been made in the Bibliographies that follow each chapter in order to keep them up to date. Fifty-six new photomicrographs have been added, and 14 of the old photomicrographs have been replaced by better ones.

It is with great regret that I record the death of Dr. Tracy B. Mallory, former chief of the Pathology Laboratory at the Massachusetts General Hospital. To him I owe a great debt of gratitude. Dr. Benjamin Castleman, the present chief of the laboratory, has advised and helped me in many ways, and I thank him. I also wish to express my thanks to Mr. Richard W. St. Clair for producing with great skill the new photomicrographs and to Mr. Walter Kahoe, Director of the Medical Department of J. B. Lippincott Company, for his many courtesies and his unfailing co-operation.

WALTER F. LEVER

Preface to the First Edition

This book is based on the courses of dermatopathology which I have been giving in recent years to graduate students of dermatology enrolled at Harvard Medical School and Massachusetts General Hospital. The book is written primarily for dermatologists; I hope, however, that it may be useful also to pathologists, since dermatopathology is given little consideration in most textbooks of pathology.

I have attempted to keep this book short. Emphasis has been placed on the essential histologic features. Minor details and rare aberrations from the typical histologic picture have been omitted. I have allotted more space to the cutaneous diseases in which histologic examination is of diagnostic value than to those in which the histologic picture is not characteristic. In spite of my striving for brevity I have discussed the histogenesis of several dermatoses, because knowledge of the histogenesis often is of great value for the understanding of the pathologic process.

Primarily for the benefit of pathologists who usually are not too familiar with dermatologic diseases, I have preceded the histologic discussion of each disease with a short description of the clinical features.

A fairly extensive bibliography has been supplied for readers who are interested in obtaining additional information. In the selection of articles for the bibliography preference has been given, whenever possible, to those written in English.

I wish to express my deep gratitude to Dr. Tracy B. Mallory and Dr. Benjamin Castleman of the Pathology Laboratory at the Massachusetts General Hospital for the training in pathology they have given me. It has been invaluable to me. Their teaching is reflected in this book. Furthermore, I wish to thank Mr. Richard W. St. Clair, who with great skill and patience produced all the photomicrographs in this book.

WALTER F. LEVER

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1

Introduction

TECHNIC FOR BIOPSY

It is important to select a proper site for biopsy. In most instances, histologic examination of a fully developed lesion will give more information than examination of an early or an involuting lesion. An exception to this rule represents vesicular, bullous and pustular lesions. For their histologic examination, a very early lesion is required; otherwise, secondary changes (such as regeneration, degeneration or secondary infection) may obscure essential features and make recognition of their mode of formation impossible. Generally, it is inadvisable to include normal tissue in the biopsy specimen, unless a large specimen is taken or the physician personally supervises the processing of the specimen, because improper sectioning by the technician may result in only normal skin being seen in the section. The specimen should include subcutaneous fat, because, in many dermatoses, characteristic histologic features are found in the lower dermis or in the subcutaneous fat. If several types of lesions are present and the diagnosis hinges on the histologic findings, much time may be saved by taking specimens for biopsy from more than one lesion.

In the author's experience, a specimen obtained with a 6-mm. biopsy punch nearly always has proved adequate for histologic study. Two sutures are sufficient to close the wound.

Before placing the specimen in the routine fixative, which in many hospitals is Zenker's or Helly's solution, one should consider which stains are desirable. Some of the special stains can be performed only if the specimen has been fixed in the appropriate fixative. A tabulation of staining methods with the required fixatives is found in Table 1, on page 29.

LIMITATIONS OF HISTOLOGIC DIAGNOSIS

Although histologic study is one of the most valuable means of diagnosis in dermatology, it has its limitations. Often, no definitive diagnosis can be made. The reason for this is that few dermatoses, aside from the tumors, are associated regularly with a diagnostic his-

tologic picture. Instead, the histologic features may be merely suggestive of a diagnosis or may be entirely nonspecific. Even in the case of tumors, difficulties in diagnosis may arise. For instance, distinction of squamous-cell carcinoma from pseudo-epitheliomatous hyperplasia is not always possible. In cases of infectious granulomas, such as syphilis, tuberculosis and the deep mycoses, a specific diagnosis often cannot be made unless the causative organism can be demonstrated. Great difficulties may also be encountered in the histologic study of the large group of noninfectious inflammatory dermatoses. In the diseases of this group, such as psoriasis, lichen planus and lupus erythematosus, in which the histologic picture is diagnostic as a rule, sometimes it may be merely suggestive. In other diseases of this group, such as the various types of dermatitis or eczema, the histologic picture is, at best, only suggestive. In still others, such as pityriasis rosea and parapsoriasis, it is always nonspecific.

Nevertheless, frequently, when the histologic picture is not diagnostic, a correlation of the histologic with the clinical findings will make a diagnosis possible.

In many instances, the chief value of histopathologic study lies in corroborating the clinical diagnosis or in ruling out possible diseases which are being considered on the basis of clinical appearance. It is obvious that the histopathologist can give the clinician a maximum amount of information only if every specimen submitted for histologic diagnosis is accompanied by detailed clinical information, including a differential diagnosis.

2

Embryology of the Skin

THE EPIDERMIS

In the earliest period of fetal life, the epidermis consists of a single layer of cells. Between the fifth and the seventh weeks of fetal life, this becomes a double layer, consisting of an inner layer, the stratum

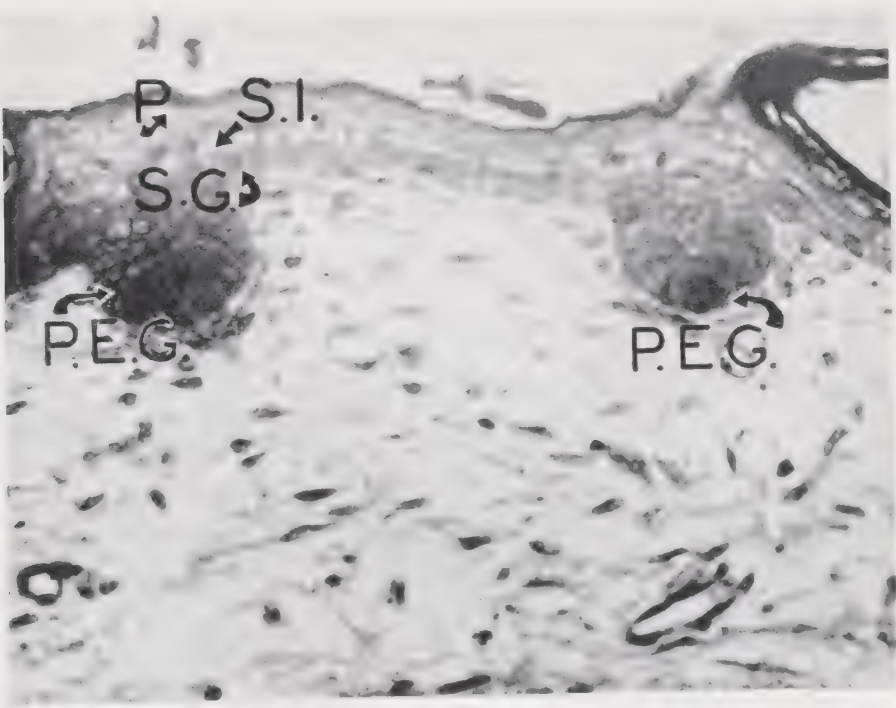


FIG. 1. The skin of an embryo 4 months old. The epidermis consists of three layers: the stratum germinativum (S.G.), the stratum intermedium (S.I.) and the periderm (P.). Two primary epithelial germs (P.E.G.) are shown. The fetal dermis shows many more fibroblasts than the adult dermis. ($\times 400$)

germinativum or palisade layer, and an outside layer, the periderm or epitrichial layer. The stratum germinativum is composed of large cuboidal cells, while the periderm consists of flat cells. In the third month, single cells appear between the two layers and later form a complete line, the stratum intermedium (Fig. 1). The cells of the

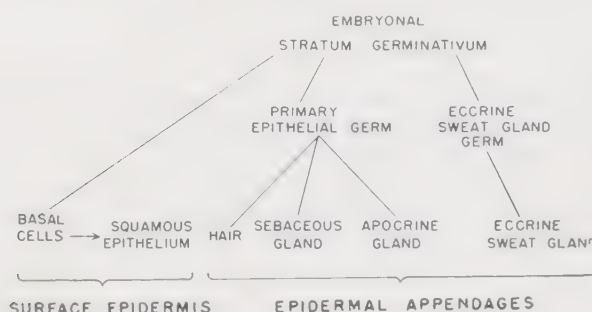
4 Embryology of the Skin

stratum intermedium are large and, because of their clear cytoplasm, have a ballooned appearance.

At about the fourth month, the periderm separates to aid in the formation of the vernix caseosa. At the same time, the stratum intermedium becomes multilayered and develops into the squamous-cell layer, or stratum malpighii. Intercellular bridges become recognizable only after the epidermis has become stratified with several layers.

The embryonal stratum germinativum differentiates into the following types of cells: (1) the basal cells, (2) the eccrine sweat-gland germ cells and (3) the primary epithelial germ cells (Chart 1).

CHART 1.—EMBRYOLOGY OF THE EPIDERMIS



Basal Cells. While the cells of the embryonal stratum germinativum possess no intercellular bridges, the mature basal cells do. By progressive differentiation, the basal cells develop into squamous cells, granular cells and horny cells, thus forming the multilayered surface epidermis.

Epidermal Appendages. The epidermal appendages develop from the primary epithelial germ cells and the eccrine sweat-gland germ cells. These cells possess no intercellular bridges and form cells without intercellular bridges. Primary epithelial germs first appear in the third month of fetal life as epithelial buds projecting into the dermis (Fig. 1). Eccrine sweat-gland germs are first observed in the fifth or the sixth month.

The eccrine sweat-gland germs give rise to the eccrine sweat glands, whereas the primary epithelial germ cells give rise to the hair matrix, the sebaceous glands and the apocrine glands. Only the hair and its two inner sheaths (the Huxley and the Henle layers) develop from the hair matrix. The outer sheath of the hair and the ducts of the sebaceous glands, which are composed of prickle cells, originate from cells with the potentiality of forming prickle cells, namely, from basal cells (Lever). The apocrine glands, which begin to form with the hair and the sebaceous gland, involute before they reach full development.

except in a few areas where they persist. (See "The Apocrine Glands," page 16.)

Melanocytes (Dendritic or Clear Cells). Whereas, in the past, the melanin-producing dendritic or clear cells were considered to be modified basal cells, there is now almost complete agreement that they are neural cells which originate in the neural crest and migrate from there with the nerves to the epidermis during early fetal life (DuShane; Rawles). Although this origin of the melanocytes has not been proved experimentally in man, it has been proved in mice by Rawles, who transplanted tissue from the neural crest of mouse embryos to the coelom of albino chicken embryos and observed the development of pigmented melanocytes.

In human embryos, argentaffine melanocytes first are identified within the epidermis early in the third month. They possess long, branching, dendritic processes which, in subsequent months, become more numerous and longer, up to 100 microns in length, joining neighboring melanocytes (Zimmermann and Cornbleet). (For a further discussion of the melanocytes, see pages 9, 12.)

THE DERMIS

The dermis is of mesodermal origin. During the first months of fetal life, it consists of closely packed spindle-shaped cells (mesenchymal cells). During the third month, fibrils appear, at first as a delicate anastomosing argyrophilic network (reticulum fibers). As the fibers increase in number and thickness, they arrange themselves in bundles which no longer can be impregnated with silver and which, instead, begin to stain with the methods for collagenous fibers (Maximow and Bloom). Simultaneously, the mesenchymal cells develop into fibroblasts. The elastic fibers appear much later than the collagenous fibers, usually in the sixth month (Lynch). The subcutaneous fat first becomes apparent in the third month.

It is not as yet settled whether collagen and elastin develop intracellularly by a direct transformation of living substance of mesenchymal cells or extracellularly by precipitation of the ground substance under the influence of an enzyme derived from mesenchymal cells. Observations on the development of fibers in tissue cultures favor the theory of their extracellular origin (Maximow and Bloom).

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3

Histology of the Skin

THE EPIDERMIS

In histologic sections of normal skin, the border between the epidermis and the dermis is irregular because of the fact that numerous cone-shaped dermal papillae reach upward and indent the inner surface of the epidermis. The ridges of epidermis separating the papillae appear in histologic sections as pegs, and, therefore, often are referred to as rete pegs although the term rete ridges is preferable.

Layers of the Epidermis. The epidermis may be divided into four layers: (1) the basal layer, (2) the stratum malpighii, (3) the granular layer and (4) the horny layer (Fig. 2). An additional layer, the stratum lucidum, is present in the epidermis of the palms and the soles, located between the granular and the horny layers. The cells in the various layers represent different stages in the gradual evolution of the basal cell into cornified cells and do not represent different types of cells.

THE BASAL LAYER. Two types of cells occur in the basal layer: basal cells and melanocytes.

Basal cells are columnar in shape and lie with their long axis vertical to the dividing line between the epidermis and the dermis. They have a deeply basophilic cytoplasm and a darkly staining oval or elongated nucleus. In sections stained with routine stains, the basal cells seem to contain melanin granules, often concentrated above their nuclei as supranuclear caps. However, Becker Jr., Fitzpatrick and Montgomery, using silver stains on separated epidermis, came to the conclusion that the melanin granules were entirely within melanocytes and that the basal cells contained none. Basal cells are united to one another and to the overlying cells by intercellular bridges (Fig. 2). These bridges are not visible as clearly as they are between the prickle cells of the stratum malpighii, but they can be demonstrated easily if the specimen is fixed immediately in Zenker's fluid and is stained with phosphotungstic acid hematoxylin (Haythorn). In some of the basal cells, mitotic figures regularly are present, denoting regeneration. However, in the normal epidermis, the lower one third

8 Histology of the Skin

of the stratum malpighii contains a greater number of mitotic figures than the basal layer (Thuringer).

The firm attachment of the epidermis to the dermis is accomplished by the firm interlocking of cytoplasmic processes of the basal cells with reticulum fibers located in the uppermost dermis. Whereas,

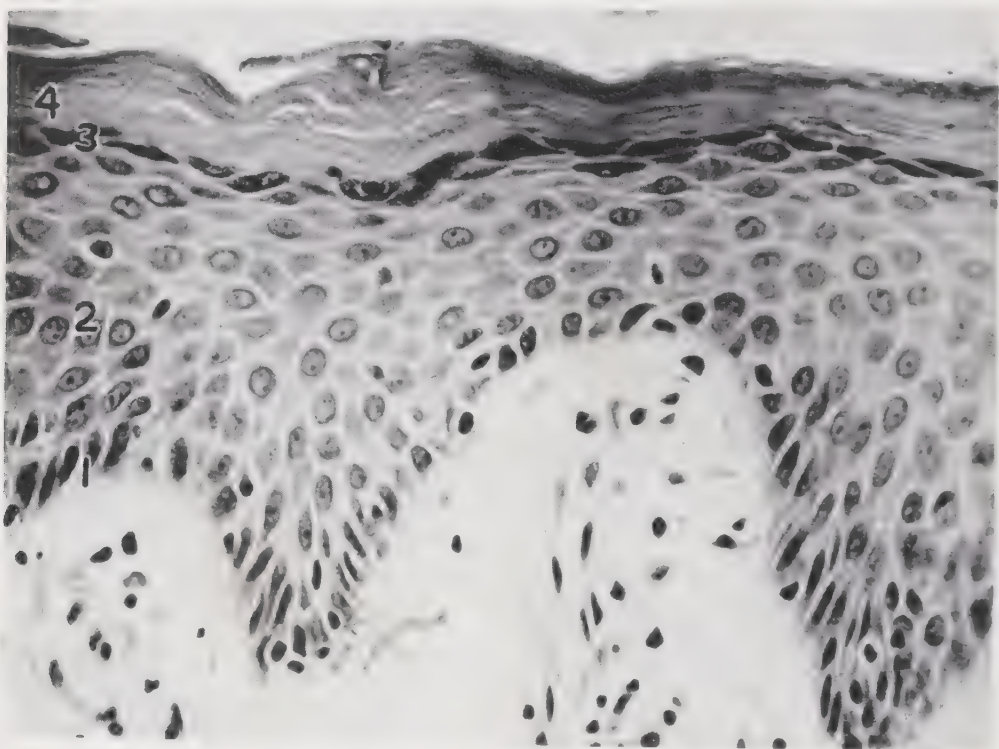


FIG. 2. Normal epidermis, dorsum of the hand. Four layers can be recognized: (1) basal layer, (2) stratum malpighii, (3) granular layer and (4) horny layer. No stratum lucidum is present. Note the presence of intercellular bridges between the basal cells. Several clear cells (melanocytes) are present in the basal layer. They possess a small dark nucleus and clear cytoplasm. ($\times 400$)

in perpendicular sections, these reticulum fibers appear like the bristles of a brush (Fig. 3), horizontal sections reveal them to form a continuous fibrillar meshwork around the cytoplasmic processes of the basal cells (Odland). In contrast with formerly expressed views, elastic fibers do not contribute to the coherence of the dermis and the epidermis since they do not extend high enough to reach the epidermis (Dick).

Whereas routine stains do not show a basement membrane, stains with the periodic acid-Schiff stain after Hotchkiss and McManus (see page 30) show a thin homogeneous dense band (Fig. 4) at the dermal-epidermal junction, indicating the presence of a relatively large amount of polysaccharide material in this zone (Stoughton and

Wells). This band represents a relative barrier to the diffusion of large particles, as proved by the fact that dye injected intradermally beneath a subepidermal bulla will not appear in the bulla fluid al-

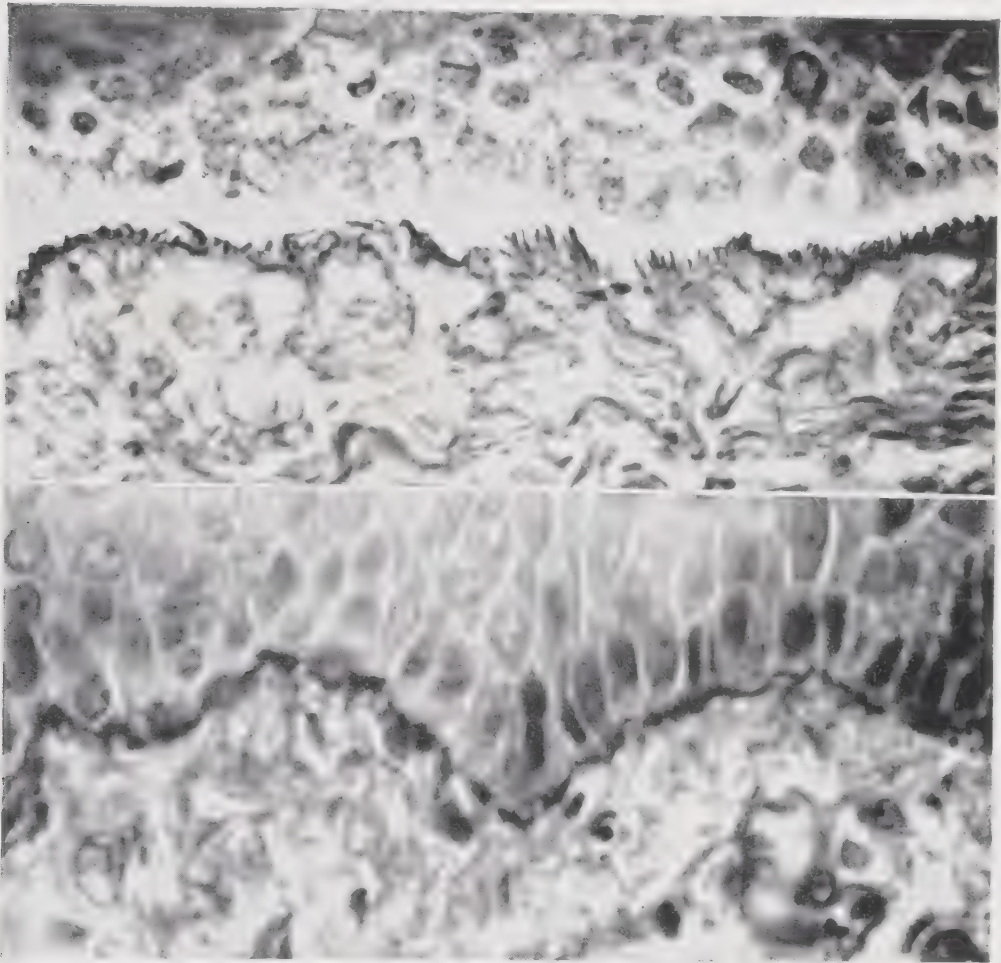


FIG. 3. (Top) Junction between the epidermis and the dermis. Foot's stain for reticulum fibers. Reticulum fibers in the uppermost dermis form a meshwork into which cytoplasmic processes of the basal cells extend. This results in a firm attachment of the epidermis to the dermis. ($\times 400$)

FIG. 4. (Bottom) Junction between the epidermis and the dermis. Periodic acid-Schiff stain of Hotchkiss and McManus. A thin, homogeneous basement membrane is located at this junction, indicated by the presence of a relatively large amount of polysaccharide material. ($\times 400$)

though it spreads readily through the dermis (Percival and Hannay). Thus, the term basement membrane probably is applicable to this band.

Melanocytes (Clear or Dendritic Cells). Melanocytes are of neural origin (see "Embryology," page 5). They stain with Bloch's dopa

stain (because they have the ability to form melanin) and usually also with silver stains (because they contain melanin) (see page 12). They also stain with gold. In sections stained with hematoxylin and eosin, melanocytes appear as clear cells having a small, dark-staining nucleus and a clear, slightly basophilic cytoplasm (Figs. 2 and 254). On the other hand, in sections impregnated with silver, they appear as dendritic cells with numerous long, branching processes, provided a sufficient amount of melanin granules are present within the processes to show their outline (Ebert; Becker Jr., Fitzpatrick and Montgomery).

THE STRATUM MALPIGHII. The cells of the stratum malpighii, which are called squamous cells or prickle cells, are polygonal and form a mosaic. They become flattened toward the surface (Fig. 2). The cells are separated by spaces which are traversed by intercellular bridges or prickles. They separate the squamous cells so that lymphatic fluid can circulate around them and supply them with nourishment. The intercellular bridges are formed by the cytoplasm of adjoining cells and tonofibrils which extend through them from cell to cell. As studies by phase contrast and polarization microscopy have shown, tonofibrils pass uninterruptedly from one cell to another all the way from the basal-cell layer to the stratum corneum. Roentgen spectography suggests that the tonofibrils consist of keratin (Nelemans, Keuning, van Rijssel and Ruiter).

Each of the intercellular bridges in the stratum malpighii contains a small nodular thickening, called the nodule of Bizzozero. These nodules are stained selectively by Heidenhain's iron-hematoxylin, which does not stain the epidermal cells and bridges (Favre). This special staining reaction suggests that the nodules of Bizzozero are special structures and not just a thickening of the intercellular bridges. Nieuwmeijer, on the other hand, believes that they merely represent an optical effect produced by the crossing of tonofibrils in the intercellular bridges.

If a gold stain is employed, one may observe, interspersed between the cells of the stratum malpighii, gold-impregnated cells with dendritic processes. These cells, called Langerhans cells, are not observed when a stain for melanin or a dopa stain is used. No agreement exists so far about their nature. Masson regards them as worn-out melanocytes which are being carried away passively toward the surface. Ferreira-Marques points out that schwannian cells generally are aurophile and, therefore, regards the Langerhans cells as schwannian cells and their dendritic processes as nerve fibers. He believes that they represent intra-epidermal receptors of pain. Becker Jr., Fitzpatrick and Montgomery, on the other hand, regard the Langerhans cells as ordinary melanocytes and maintain that they appear to lie in the

superficial epidermis only because of distortion and wrinkling of the tissue produced by the acid used in the gold impregnation. In separated epidermis, which is less distorted by acid than whole skin, they found gold-impregnated cells only at the junction of the epidermis and the dermis and never in the upper layers of the epidermis.

THE GRANULAR LAYER. The cells of the granular layer are diamond-shaped and filled with granules (Fig. 2). The granules are

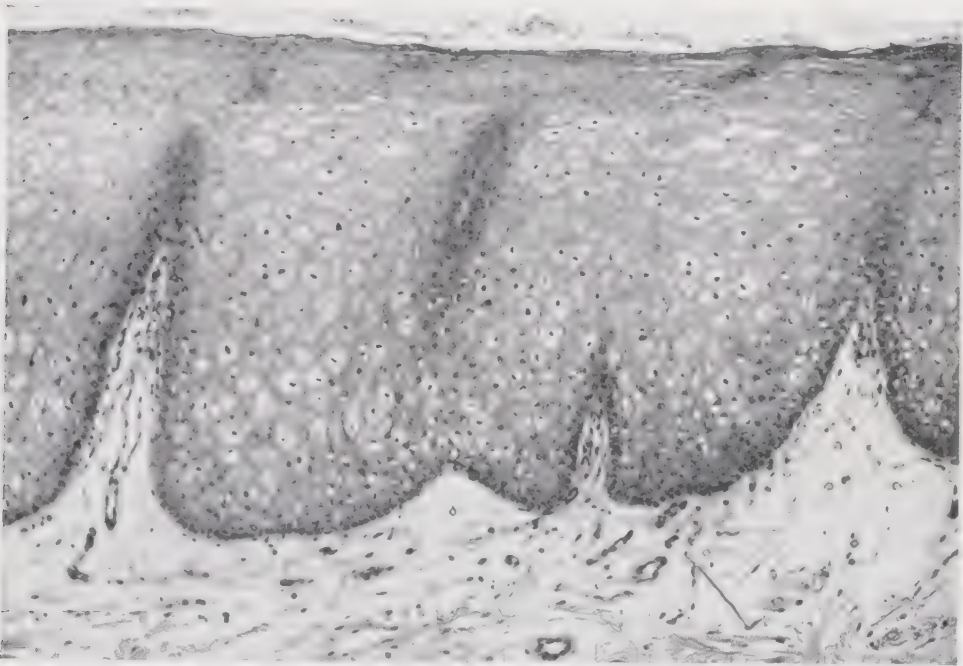


FIG. 5. Epithelium of the oral mucosa. No keratin is formed. The epithelial cells in their migration from the basal layer to the surface first become vacuolated, then shrink and finally desquamate. ($\times 200$)

coarse, irregular in size and shape, and strongly light-refractile. The chemical nature of the granules is not known. Unna called them keratohyaline granules, but the substance differs in its chemical behavior from both keratin and hyalin. The thickness of this layer varies from one to three cells and stands, as a rule, in direct relation to the degree of keratinization. The layer is thickest in areas where the stratum corneum is developed most highly. In areas of imperfect keratinization (parakeratosis), the granular layer is usually absent.

THE HORNY LAYER. The thickness of this layer varies from 0.02 mm. on the flexor surface of the forearm to 0.5 mm. and more on the soles. No intercellular spaces exist between the horn cells; they are closely united. Under normal conditions, no nuclei are present in this layer.

The mucous membrane of the mouth normally possesses no gran-

ular cells and no horny layer. There the epithelial cells in their migration from the basal layer to the surface first become vacuolated, then shrink and finally desquamate (Fig. 5).

THE STRATUM LUCIDUM. This layer occurs only on the palms and the soles. It is located above the granular layer and is composed of two or three layers of flat, anuclear cells of homogeneous, transparent appearance. The substance filling the cells and giving them the oily appearance is called eleidin, which is believed to be formed by liquefaction of the keratohyaline granules. Ordinarily, this layer cannot be demonstrated in sections stained by routine staining methods. However, it can be shown by two rather complicated staining methods described by MacLeod and Muende.

Pigment of the Epidermis. For the study of cutaneous pigmentation, two stains are necessary: the silver stain and the dopa stain. Silver stains melanin black, thus indicating its presence. Dopa stains those cells dark which contain the enzyme tyrosinase and thus possess the ability to form melanin. Such cells represent melanocytes and stain dark regardless of whether or not they actually contain melanin. The dopa stain technic, originated by Bloch (1925), and refined by Becker, Prayer and Thatcher, consists in bathing sections of skin in a 0.1 per cent solution of levorotatory 3,4-dihydroxyphenylalanine (called "dopa" for short). Following Bloch's suggestion, the cells that stain dark with the dopa stain are called dopa-positive. Such cells stain dark because the enzyme tyrosinase which they contain changes the colorless dopa of the stain into a dark insoluble product, the dopa melanin (Bloch, 1927). The dopa stain closely imitates physiologic melanin formation, which occurs because the amino acid tyrosine in cells containing the enzyme tyrosinase is transformed to dopa and further to melanin by the action of this enzyme (Lerner and Fitzpatrick).

The dopa stain shows that in the basal layer only the neural melanocytes (dendritic or clear cells) are dopa-positive. The epidermal basal cells do not form melanin; they therefore are dopa-negative. Dopa-positive melanocytes not only are present in the basal layer of the epidermis but also are found interspersed between the hair matrix cells of the hair bulb. When active melanin formation occurs (e.g., after exposure to the sun), the number of dopa-positive melanocytes in the basal layer of the epidermis increases greatly.

The silver stain does not, like the dopa stain, demonstrate the site of formation of melanin, but instead demonstrates the presence of melanin. Thus, in the presence of melanin, not only melanocytes but also mesodermal phagocytic cells, so-called melanophores or chromatophores, stain positive with silver. In a lightly pigmented epi-

dermis, melanin is seen only in the region of the basal layer. However, in a deeply pigmented skin, as in the Negro, melanin is found also in the upper layers of the epidermis and in phagocytic cells of the dermis. Studies by Becker Jr., Fitzpatrick and Montgomery on separated epidermis have revealed that even in deeply pigmented skin melanin is never found in basal cells or squamous cells. It is contained exclusively in melanocytes and their dendritic processes until the stratum granulosum is reached. At this level the dendrites terminate and free melanin granules are seen in the granular layer and the stratum corneum.

The Nerves of the Epidermis. The technic of staining nerve fibers intravitaly with methylene blue has added greatly to the knowledge of cutaneous innervation. By this method, as well as by impregnation with reduced silver, intra-epidermal terminal nerve fibers mediating pain have been demonstrated extending upward from the dermis into the lower layers of the stratum malpighii and, in the fingers, even into the stratum granulosum (Woollard, Weddell and Harpman). With the methylene blue method, these nerve fibers subserving pain have a characteristic beaded appearance. In addition, there are in the lower epidermis the Merkel's disks which are small intercellular structures representing receptors of touch. They are most abundant on the fingers, where they may show connections by means of medullated fibers with Meissner's tactile corpuscles located in the papillae (Woollard).

Formerly, two types of cells within the epidermis were regarded as nerve end cells: the Merkel-Ranvier tactile cells and the Langerhans cells. The Merkel-Ranvier cell is identical with the clear cell and as such is a melanocyte. While the nature of the Langerhans cell is still under dispute, those who regard it as a nerve end cell are in the minority (see page 10).

THE EPIDERMAL APPENDAGES

The Sweat or Eccrine Glands. Sweat glands are present everywhere in the human skin. They are found in greatest abundance on the palms and the soles and in the axillae. They are tubular glands whose secretory cells during the process of secretion do not change in size or shape and do not release any cellular material into the lumen of the gland. Schiefferdecker called the sweat glands eccrine glands because of his belief that their secretory cells simply excrete.

Sweat glands are composed of a secretory and a ductal portion. The secretory portion lies coiled up either at the border between the dermis and the subcutaneous fat or in the lower third of the dermis (Fig. 6). When located in the lower dermis, it is surrounded by fatty

tissue which connects with the subcutaneous fat. Although eccrine glands are formed embryologically with two layers of epithelial cells throughout, only one distinct layer, composed of secretory cells, lines



FIG. 6. Normal skin, back of neck. On the left side of the illustration, a sweat duct (S.D.) enters the epidermis. In the center, a large sebaceous gland (S.G.) leads into a follicle containing a lanugo hair. On the right side, a large hair (H.) lies within a follicle surrounded by sebaceous glands. An arrector pili muscle (A.P.) is situated in the obtuse angle of the hair. Beneath the large sebaceous gland, a coiled-up eccrine sweat gland (S.W.G.) is present. ($\times 50$)

the secretory portion in postembryonal life (Fig. 7), because the second, outer layer of epithelial cells has become differentiated into myo-epithelial cells. The secretory cells are large, cylindrical cells with clear, slightly basophilic cytoplasm. The myo-epithelial cells are small, spindle-shaped cells inserted sporadically between the secretory cells at their bases. Their long axis extends at a right angle to that of the secretory cells, i.e., parallel with the circumference of the

gland. They possess long processes composed of cytoplasmic fibrils with the same staining properties as smooth muscle and are contractile. By their contraction, they drive the secretion out of the secretory cells into the lumen. Peripheral to the myo-epithelial cells lies a thin hyaline basement membrane.

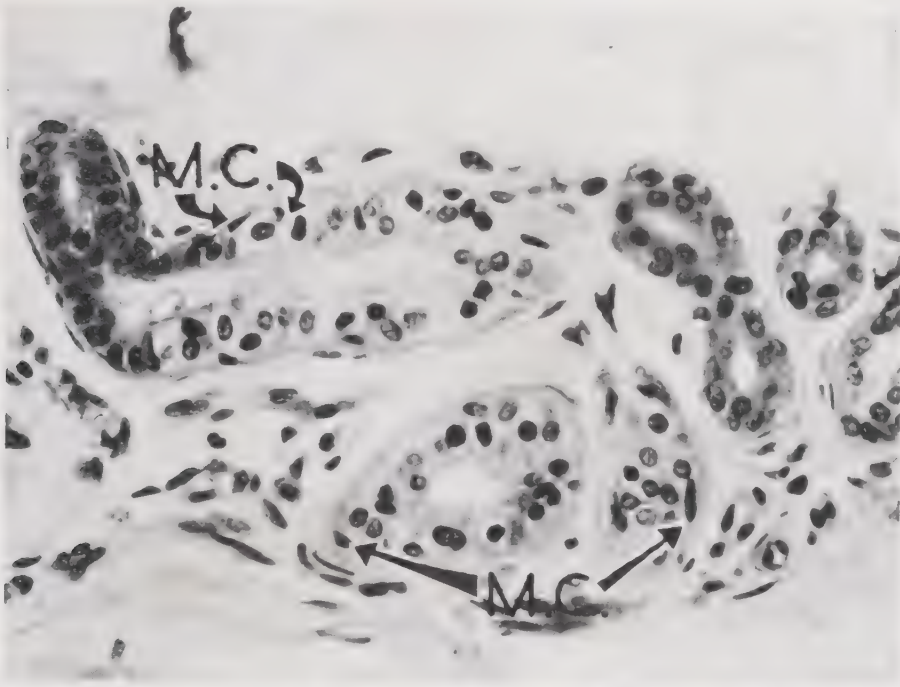


FIG. 7. Eccrine sweat glands and ducts. In the center three glands, on the right side three ducts, are shown. On the left side, a duct leads out of a gland. The glands are composed of only one layer of large, pale cells. Here and there small myo-epithelial cells are wedged in at their bases (M.C.). The ducts are composed of two layers of small, cuboidal, dark-staining cells. The lumina of the ducts are lined with a homogeneous cuticle. ($\times 400$)

The ductal part of the sweat glands leads into the epidermis (Fig. 6). Up to the epidermis, the duct is composed of two layers of small, cuboidal, deeply basophilic epithelial cells. No peripheral basement membrane is present, but the lumen of the duct is lined with a deeply eosinophilic, homogeneous membrane or cuticle. Some authors state that the duct loses its own lining epithelium when it enters the epidermis and that the wall within the epidermis is composed of prickle cells in circular arrangement (Way and Memmesheimer, 1936). Others, however, like Pinkus, maintain that sweat ducts have their own lining cells within the epidermis. The observation by Holyoke and Lobitz that the cells lining the intra-epidermal portion of the

sweat duct maintain their normal structure when surrounded by carcinoma tends to support Pinkus' contention.

The lumen of sweat glands is small, measuring approximately 20 microns in diameter in the secretory portion, and less still in the ductal portion. In the horny layer of the epidermis, it measures only from 5 to 10 microns in diameter. (The diameter of an erythrocyte is 7.6 microns.)

The Apocrine Glands. The apocrine glands differ from the eccrine glands in origin, distribution, mode of secretion, size and staining reactions. They represent vestigial scent glands.



FIG. 8. Apocrine glands and eccrine sweat glands in the axilla. Note the great difference in the size of the lumina of the apocrine glands (*left*), and of the eccrine glands (*right*). The apocrine gland cells show "decapitation secretion." ($\times 100$)

Apocrine glands originate, together with hair and sebaceous glands, from the primary epithelial germ (see page 4). Accordingly, the ducts of the apocrine glands lead into pilosebaceous follicles and not directly to the epidermis.

Apocrine glands are encountered in only a few areas: in the axillae, around the nipples, in the perigenital and the perianal regions, and, as modified glands, in the external ear canal (ceruminous glands), in the eyelids (Moll's glands) and in the breast (mammary glands). Occasionally, a few apocrine glands are found on the abdomen and the chest.

Apocrine glands are tubular, actively secreting glands whose secretory cells pass through a full cycle of secreting stages. They are low cuboidal at the beginning of the cycle, gradually increase in height until they protrude into the lumen and then release part of their cytoplasm into the lumen (Fig. 8). This mode of secretion has been referred to by Schiefferdecker as decapitation secretion. He chose the name apocrine for these glands because part of the cytoplasm of their secretory cells is pushed off ("apo" = off).

The lumen of the secretory portion of the apocrine glands is large, measuring up to 200 microns in diameter. This is 10 times the average diameter of the lumen of the sweat glands.

The secretory portion has only one distinct layer of epithelial cells because the outer layer has become differentiated, just as in the sweat glands, into myo-epithelial cells. The secretory cells vary greatly in height, depending on the stage of their secretory cycle. The secretory cells stain distinctly eosinophilic in contrast with the secretory cells of sweat glands, which stain slightly basophilic. In addition, they frequently contain granules which react positively to iron stains (Homma). The lumen of the apocrine glands is filled with cellular detritus as a result of the decapitation secretion. The duct is lined by two layers of epithelial cells, which stain slightly eosinophilic, in contrast with the cells of the sweat duct, which stain deeply basophilic.

The Sebaceous Glands. Sebaceous glands are present everywhere on the skin except on the palms and the soles. They are present also on the modified skin of the vermilion border of the lips, the glans penis, the inner surface of the prepuce, the labia minora and the clitoris. Sebaceous glands are alveolar, holocrine glands—that is, they have no lumen and their secretion is formed by decomposition of their cells. The secretion is evacuated through the sebaceous duct into a pilosebaceous follicle (Fig. 6). From one to six sebaceous glands are grouped around and discharge into each pilosebaceous follicle. On ordinary skin the pilosebaceous follicle may or may not contain a hair. On modified skin, where hair is absent, sebaceous glands lead into follicles devoid of hair. The meibomian glands of the eyelids are modified sebaceous glands.

Each sebaceous gland is composed of several lobules. Each lobule has at its periphery one layer of deeply basophilic cuboidal cells, the generative cells (Grynfeldt). All cells inward from this layer have their cytoplasm arranged in a delicate network. The meshes of this network are filled by fat, which is predominantly neutral fat. As such, it is isotropic and does not illuminate on polariscopic examination when the disks are crossed (see page 31).

Hair. The hair consists of the hair shaft, composed of keratinized cells, and the hair root, composed of nonkeratinized cells. The hair root terminates in a knoblike expansion, the hair bulb, containing the hair matrix cells. A small connective-tissue structure, the papilla,

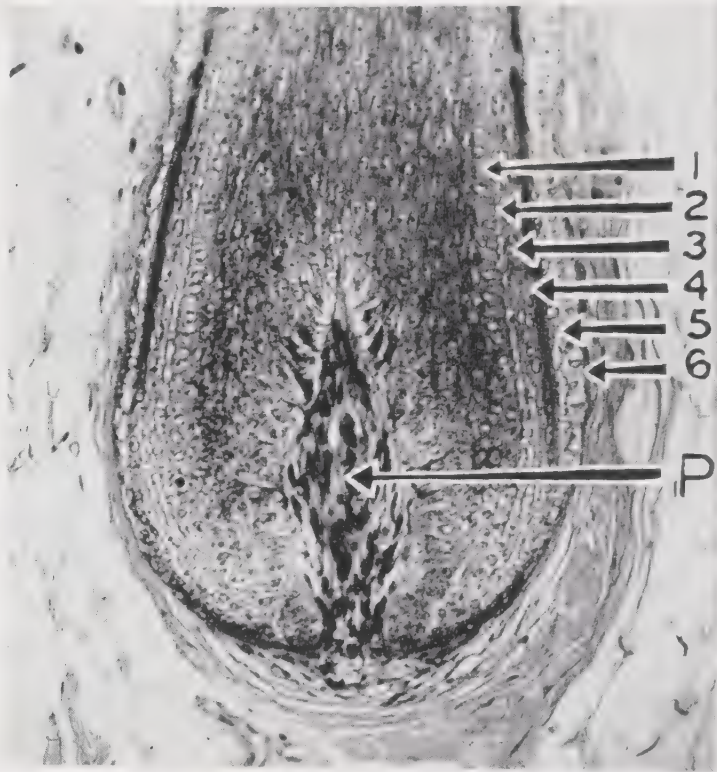


FIG. 9. Lower part of a hair. The hair papilla (P), composed of connective tissue, protrudes into the hair bulb. The various linings of the hair can be recognized. They are, from the inside to the outside: (1) the hair cuticle, (2) the sheath cuticle, (3) the Huxley layer, (4) the Henle layer (which stains darkly), (5) the outer hair sheath and (6) the vitreous layer. ($\times 200$)

protrudes into the hair bulb (Fig. 9). The papilla is richly supplied with blood vessels and nerves and, in individuals with dark hair, contains considerable amounts of melanin situated largely in macrophages.

Each hair is surrounded by two inner sheaths and an outer sheath, all composed of epithelial cells. The two inner sheaths develop, together with the hair, from hair matrix cells, while the outer sheath represents a downward extension of the epidermis.

The hair root consists of a medulla and a cortex. Its cells possess large, vesicular nuclei and contain variable amounts of melanin. Dopa-positive melanocytes are interspersed between the hair cells

where the hair rests on the papilla. Peripheral to the cortex is the hair cuticle, which is composed of a single row of nucleated cells (Fig. 9, ₁).

The hair shaft is composed of fully keratinized cells closely united with one another and containing either no nuclei or elongated, greatly shrunken nuclei. No medulla and no hair cuticle are recognizable since they have lost their identity in the process of keratinization. It may be pointed out that keratinization in the hair proceeds without the interposition of granular cells.

The two inner hair sheaths accompany the hair to approximately the level at which keratinization begins. They are separated from the hair cuticle by the sheath cuticle (Fig. 9, ₂). The sheath cuticle consists of a single layer of cells which are interlocked tightly with the cells of the hair cuticle. The two inner hair sheaths are from inside to outside, the Huxley layer (Fig. 9, ₃) and the Henle layer (Fig. 9, ₄). The Huxley layer consists of two or three rows of cells which stain rather lightly and contain only a few scattered trichohyaline granules. The Henle layer consists of one or two rows of cells, which stain darkly because they are filled completely with trichohyaline granules. On this account the nuclei are difficult to recognize, and some authors have even stated that the Henle layer contained no nuclei. However, they can be recognized easily in hair cut on a diagonal plane.

The outer hair sheath (Fig. 9, ₅) extends from the epidermis downward to the sides of the hair bulb, where it ends. It is thickest near the epidermis and gradually decreases in thickness toward the hair bulb. Its cells have a clear, vacuolated appearance due to the presence of considerable amounts of glycogen in the cytoplasm. Outside of the outer hair sheath lies a thin membrane of condensed connective tissue, the glassy or vitreous layer (Fig. 9, ₆).

Nails. The nail is composed of keratin. It grows from the nail matrix which is located beneath the nail fold. The nail matrix consists of epidermis without a stratum granulosum. Thus, just as in the hair, keratinization in the nail proceeds without the interposition of a granular layer. The epithelium of the nail bed has no stratum granulosum either. Its rete ridges are oriented not as a network of anastomosing ridges, as elsewhere in the skin, but as parallel longitudinal ridges.

THE DERMIS

Three types of fibers occur in the dermis: collagenous, elastic and reticulum fibers.

Collagenous Fibers. Collagen forms more than 98 per cent of the connective tissue of the dermis. It occurs in bundles of fibers held

together by an interfibrillary ground substance. The fibers and the bundles are coarsest toward the subcutaneous tissue and finest toward the outermost portion of the dermis. In the papillary and the subpapillary portions of the dermis, the collagen bundles run in an apparently haphazard manner and do not interlace. In the lower dermis, the bundles are arranged nearly parallel to the surface of the skin and do interlace. Collagen bundles are only slightly extensible, but, since they are wavy, they permit stretching of the skin. A small number of cells, the fibroblasts, are interspersed between the collagen bundles. They have oval or spindle-shaped, pale nuclei endowed with a distinct nuclear membrane (see page 36).

Elastic Fibers. The collagen bundles are interwoven with a web of elastic fibers. The elastic fibers are slightly wavy, and, therefore, only a small portion of any fiber is seen in any histologic section. The fibers are thickest and densest in the lower portion of the dermis, where they are arranged, just as the collagen bundles, chiefly parallel to the surface of the skin and are up to 200 microns long. In the uppermost dermis, there are only few small fibers running horizontally, obliquely and sometimes vertically. From these fibers, still finer fibrils spread out toward the epidermis but do not reach it (Dick). Therefore, elastic fibers do not contribute to the attachment of the epidermis to the dermis, as had been believed formerly. Routine stains, such as hematoxylin-eosin and phloxine-methylene blue, do not stain the elastic fibers, and selective elastic tissue stains, such as Verhoeff's stain, must be employed. The elastic fibers are rigid, not elastic; but, because of their rigidity, they effect the return of the skin into its normal position after stretching, thus supplying elasticity to the skin. Their rigidity prevents overdistention. When the skin is overstretched, as in pregnancy, the elastic fibers may break and degenerate.

Reticulum Fibers. Reticulum fibers (or lattice fibers, "Gitterfasern") form a third system of fibers. They are not visible as such with routine stains but stain with silver (Foot's stain). It now is agreed quite generally that reticulum is immature collagen ("pre-collagen"), or collagen occurring as separate fibrils, and that collagen is merely compacted reticulum (Mallory and Parker). One easily can see, in sections containing reticulum fibers and stained with Foot's stain, that in areas where the reticulum fibers are densest they tend to aggregate into collagen bundles (Fig. 89). The essential identity of collagen and reticulum is based on the fact that both react alike to all stains with the exception of silver stains (Mallory and Parker). The difference in argyrophilic properties is due to the fact that reticulum fibrils are finer than collagen fibrils and therefore

are penetrated more easily by the colloidal silver (Nageotte and Guyon).

Reticulum fibers probably are formed by gelation of an extracellular substance secreted by mesodermal cells (Foot and Day). Various types of mesodermal cells have the ability to form reticulum fibers, namely, reticulum cells, histiocytes, lymphocytes, vascular endothelial cells, smooth as well as striated muscle cells and fat cells (Dublin).

The normal skin contains only a few reticulum fibers, since all the reticulum is present in a mature state condensed to collagen. A few reticulum fibers usually are recognizable around the glandular parts of sweat glands and around the blood vessels. In addition, reticulum fibers are present in the uppermost dermis (Fig. 3). In perpendicular sections, these reticulum fibers appear arranged like the bristles of a brush; but horizontal sections show a continuous fibrillar meshwork (Odland). Due to the fact that cytoplasmic processes of the basal cells extend into this meshwork, a firm coherence between the dermis and the epidermis is brought about (see page 8).

In contrast with the sparsity of reticulum fibers in normal skin is the abundance of reticulum fibers in pathologic conditions in which there is formation of young mesodermal cells. Large amounts of reticulum fibers are present in granulomas, such as tuberculosis, sarcoid (Fig. 89) and syphilis, and in mesodermal tumors, such as histiocytomas, sarcomas and lymphomas. However, if the mesodermal cells are very immature, as in stem-cell lymphoma, they may not possess the ability to form reticulum fibers; and if the mesodermal cells are very mature, as in some fibromas, all newly formed reticulum fibers may have become condensed to collagen.

Nerves and Nerve End Organs. On sections stained by routine methods, one easily can recognize the large nerves and the Pacini and Meissner end organs. The fine nerves and the other nerve end organs require special staining: either impregnation with silver salts, e.g., by the Bodian stain (Bodian), or vital staining with methylene blue (Woollard, Weddell and Harpman).

The skin is endowed with nerves from both the cerebrospinal and the autonomic, or vegetative, system. The sensory nerves belong to the cerebrospinal system, while the vasomotor nerves and the nerves supplying the smooth muscles and the sweat glands belong to the autonomic system. The sebaceous glands are not supplied with nerve fibers and their functioning depends on endocrine stimuli. Cerebrospinal and autonomic nerves can be differentiated to a certain degree, since the former up to their terminal ramifications always possess a myelin sheath while the latter usually do not. A few sympathetic fibers may possess a myelin sheath (Jaeger).

The basic unit of any nerve is the neurofibril, several of which form a neurite or axon. An axon may or may not have a myelin sheath, but always is surrounded, except at its terminal ramifications, by the neuro-ectodermal schwannian sheath and the mesodermal endoneurium. In medium-sized nerves, several such units are bound together by the perineurium. Large nerve trunks have several such components and an epineurium as a cover. All autonomic nerves and



FIG. 10. Pacini corpuscles in the subcutaneous fat of a fingertip. Their largeness becomes apparent if one compares their size with that of the eccrine sweat glands and their ducts which are located on the right side of the field. ($\times 50$)

most cerebrospinal nerves end freely in numerous ramifications. However, some of the latter end in special nerve end organs.

Nerve end organs are not present to an equal degree everywhere. They abound in areas of refined sensations, such as the palms and the soles, the lips and the genital region, and are sparse elsewhere. The function of some is not established clearly. Several types of nerve end organs occur: the Pacini bodies, the Meissner tactile bodies, the Ruffini bodies, the Krause bodies and the genital corpuscles. These end organs all have a similar structure: a connective-tissue capsule surrounding a core in which the afferent nerve splits up into numerous branches.

PACINI CORPUSCLES. The Pacini corpuscles are the largest of the end organs. They measure up to 2 mm. in diameter and thus are

detected easily in microscopic sections (Fig. 10). Located in the subcutis, especially of the palms and the soles, they aid in the mediation of the sense of pressure. They are large, oval, onionlike structures composed of a cortex, a core and a myelinated nerve which enters the structure at its lower pole. The cortex consists of from 20 to 60 concentric layers of fibrous tissue; the core consists of semisolid material in which the nerve is embedded. The myelin sheath accompanies the nerve up to the upper pole of the Pacini corpuscle. There the nerve ends in numerous ramifications.

MEISSNER TACTILE BODIES.

These are located in papillae (Fig. 11) and mediate a sense of touch. They are present almost exclusively on the hands and the feet and are especially numerous on the palmar surfaces of the fingers, with their number increasing distally. On the finger tips, they lie in groups of two or three in adjoining papillae, thus supplying a spatial relationship to the sense of touch (Weddell). They are cone-shaped and lie with their long axis perpendicular to the surface of the skin. They are of such size that they occupy the greater part of the papilla in which they are located. They are composed of a connective-tissue capsule and flat-

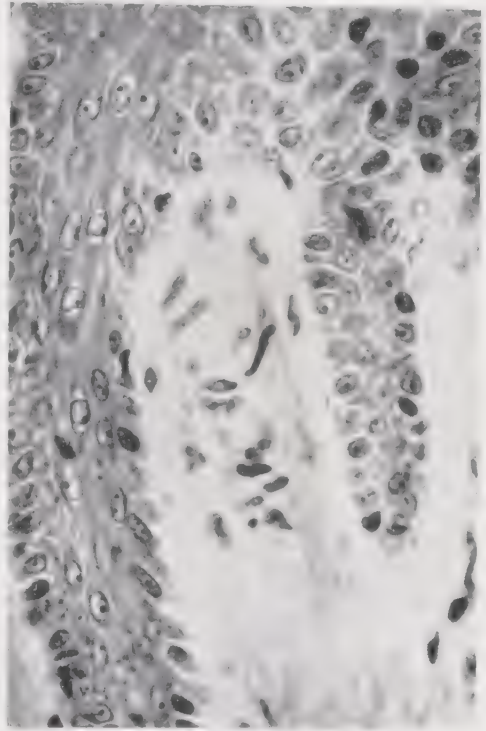


FIG. 11. A Meissner tactile body located in a papilla of the fingertip. It is composed of flattened (schwannian) cells which have their longest diameter in a transverse direction. Since this is a hematoxylin and eosin stain, the nerve fibrils cannot be visualized. ($\times 400$)

tened cells, probably schwannian cells, which have their longest diameter in a transverse direction. One to four myelinated nerves lead to each body. They lose their myelin sheath on entering the body and divide into fibrils which pass upward in a spiral fashion.

RUFFINI BODIES. The Ruffini bodies are located in the deeper dermis and in the subcutis. Some believe that they mediate a sensation of heat. They present brushlike ramifications of a nonmyelinated nerve within a thin connective-tissue capsule.

KRAUSE BODIES. The Krause bodies are irregularly shaped spherical formations located in the dermis close to the epidermis. They

have a thin fibrous capsule within which nonmyelinated nerves branch. They are believed to mediate a sensation of cold.

GENITAL CORPUSCLES. These have the same general structure as the Krause bodies, but are larger and have a thicker capsule.

MERKEL-RANVIER TACTILE CELLS. These cells, located in the epidermis, are discussed on page 13.

Blood Vessels. The arrangement of the cutaneous blood vessels is inconstant and varies in different parts of the skin. Nevertheless, a deep plexus at the junction of the dermis and the subcutaneous tissue and a superficial plexus in the subpapillary layer are always present. The deep plexus has arterioles which possess three layers: adventitia, media and intima. The media and the adventitia gradually become thinner as the arteriole ascends through the dermis. The capillaries in the papillary layer are composed merely of one layer of endothelial cells surrounded by a few histiocytes (perithelial cells). In some instances, an additional type of cell, called the pericyte, is present. This cell has branching processes which encircle the capillary and are contractile. They can thus change the caliber of the lumen. They represent modified smooth muscle cells (Stout and Murray).

A special structure, the glomus, is distributed widely throughout the dermis, but occurs most abundantly on the tips of the fingers and the toes and in the nailbeds. The glomus is concerned with temperature regulation and represents a special short-circuit device connecting, without the interposition of capillaries, an arteriole with a venule. It consists of an arterial and a venous segment. The arterial segment, called the Sucquet-Hoyer canal, branches from an arteriole and has a narrow lumen and a thick wall. The wall consists of an inner endothelial layer and of several layers of glomus cells, which are large cells with clear cytoplasm resembling epithelioid cells. The glomus cells are in intimate association with a rich network of nonmyelinated nerve fibrils demonstrable by silver stain. Although myofibrils are sparse or absent in the glomus cells, they are contractile. The glomus cell generally has been regarded as a modified smooth muscle cell (Popoff; Weidman). On the basis of tissue culture experiments, Murray and Stout believe that the glomus cell is derived from the pericyte. The venous segment of the glomus has a wide lumen. The blood is emptied from the venous segment into subpapillary venules and through the latter into deeper veins.

Lymphatic Vessels. Lymphatic fluid circulates in the epidermis around the squamous cells, which are kept apart by intercellular bridges or prickles. Similarly, lymphatic fluid circulates between the

collagen bundles. Lymphatic vessels begin as loops in the papillae and lead down to a lymphatic plexus in the subpapillary layer, from which they pass down through the dermis to a deeper plexus at the junction of the dermis and the subcutis. Lymphatic vessels are lined by only one layer of endothelial cells.

Muscles of the Skin. Smooth or involuntary muscle is characterized by the absence of striation in the muscle fibers and by the location of the nuclei in the center of the muscle fibers. The arrectores pilorum, the tunica dartos of the scrotum and the muscle fibers in the areola of the nipple are smooth muscles. The muscle fibers of the arrectores pilorum are anchored in the connective tissue of the papillae and are attached to the hair follicles below the sebaceous gland. They are situated in the obtuse angle of the follicle, so that, on contracting, they make the follicle more vertical and produce "gooseflesh" (Fig. 6).

Striated or voluntary muscle shows cross-striation of its fibers. The nuclei are located at the periphery of the fibers. Striated muscle is found in the skin of the neck (platysma) and the face (muscles of expression).

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4

Laboratory Methods

FIXATION, EMBEDDING AND STAINING

Fixation. Helly's fixative is used routinely in the Pathology Laboratory of the Massachusetts General Hospital. For its preparation two solutions are required: (1) Zenker's solution

Potassium dichromate	2.5 Gm.
Mercury bichloride	8.0 Gm.
Water	100.0 cc.

and (2) Formalin (which is a 40 per cent aqueous solution of formaldehyde). Formalin 1 cc. is added to each 20 cc. of Zenker's solution just before use. The specimen should remain not less than 5 hours and not longer than 24 hours in Helly's fixative. It is then washed in running water for at least 2 hours and transferred into 80 per cent alcohol, in which it can be left indefinitely.

For specimens which have to be mailed, the fixative of choice is 10 per cent Formalin because specimens may remain in this fixative indefinitely. One cc. of Formalin is added to each 9 cc. of water just before use.

Helly's fixative is contraindicated if one desires to demonstrate lipids, nerve fibers, amyloid, granules of mast cells, spirochetes, calcium or mucin, or if one wishes to perform a dopa stain. For the demonstration of lipids, nerve fibers, amyloid, granules of mast cells and spirochetes, fixation in 10 per cent Formalin is required; to demonstrate calcium, 80 per cent alcohol is used; and for demonstration of mucin, absolute alcohol is the approved fixative. For the dopa stain, no fixative should be employed; the fresh tissue should merely be wrapped in moist gauze and sent to the laboratory.

Dehydrating and Embedding. Following fixation, all routine specimens are placed successively into several beakers containing dioxane in increasing concentrations for dehydration and several beakers of hot paraffin for embedding. This may be done by hand or with the aid of an Autotechnicon machine.

In the Pathology Laboratory of the Massachusetts General Hospital, as in most other such laboratories, all routine specimens,

TABLE 1.—SURVEY OF STAINING METHODS EMPLOYED AT THE MASSACHUSETTS
GENERAL HOSPITAL

FIXATION AND EMBEDDING	STAIN	PURPOSE OF STAIN	RESULTS
Helly's—paraffin (Autotechnicon)	Hematoxylin and eosin	Routine	Nuclei blue; collagen, nerves, muscle red
Helly's—paraffin (Autotechnicon)	Phosphotungstic acid-hematoxylin	Nuclear details and for distinction of collagen and muscle	Nuclei, nerves, muscle blue; collagen brown
Helly's—paraffin (Autotechnicon)	Aniline blue (Mallory)	Collagen	Nuclei, nerves, muscle bright red; collagen blue
Helly's—paraffin (Autotechnicon)	Masson's tri-chrome	Collagen	Nuclei, nerves, muscle dark red; collagen green
Helly's—paraffin (Autotechnicon)	Van Gieson	Collagen	Collagen red; nuclei, nerves, muscle yellow
Helly's—paraffin (Autotechnicon)	Verhoeff	Elastic tissue	Elastic tissue black
Helly's—paraffin (Autotechnicon)	Foot	Reticulum	Reticulum and neurofibrils black
Helly's—paraffin (Autotechnicon)	Potassium ferrocyanide	Iron	Iron blue
Helly's—paraffin (Autotechnicon)	Giemsa	Eosinophils, bacteria, Donovan bodies, <i>Leishmania</i> , Frisch bacilli, <i>Histoplasma capsulatum</i>	Bacteria blue; granules of eosinophils, Donovan bodies, <i>Leishmania</i> , Frisch bacilli, <i>Histoplasma capsulatum</i> brilliant red
Helly's—paraffin (Autotechnicon)	Gram	Bacteria	Gram-positive bacteria blue; Gram-negative bacteria red
Helly's—paraffin (Autotechnicon)	Ziehl-Neelsen Fite	Acid-fast bacteria	Acid-fast bacteria red Acid-fast bacteria black
10% Formalin—paraffin	Levaditi	Spirochetes	Spirochetes black
10% Formalin—paraffin	Bodian	Nerves	Neurofibrils black
10% Formalin—paraffin	Methylene blue Giemsa	Granules of mast cells	Mast cell granules purple
10% Formalin—frozen section	Scarlet red	Lipids	Neutral fat bright orange; cholesterol brownish red
10% Formalin—frozen section	Crystal violet	Amyloid	Amyloid purple
Absolute alcohol—celloidin	Mucicarmine	Mucin	Mucin red
80% alcohol—paraffin	Von Kossa	Calcium	Calcium black
Fresh tissue—frozen section	Dopa	Melanin-producing cells	Melanin-producing cells show dark granules

whether unfixed or already placed in Helly's fixative or in 10 per cent Formalin, are sent through the Autotechnicon. This machine, which is controlled by an electric clock, accomplishes fixation, dehydration and embedding automatically overnight. The specimens are placed in small, perforated cassettes, which are then put into a perforated metal basket suspended from an arm of the machine. The metal basket is automatically lowered into and raised out of a succession of beakers containing Helly's fixative, water, 95 per cent alcohol, dioxane and warm liquid paraffin.

Specimens that are to be stained for lipids, nerve fibers, amyloid, calcium, mucin, spirochetes or granules of mast cells, or are to be treated with the dopa stain, are not sent through the Autotechnicon, in order to avoid exposure to Helly's fixative. Specimens to be stained for nerve fibers, calcium, granules of mast cells or spirochetes, after fixation, are carried by hand through dioxane and embedded in paraffin. Specimens to be stained for mucin, after fixation, are embedded in celloidin. Specimens to be stained for lipids or amyloid, after fixation, are cut on the freezing microtome and then stained. Specimens to be stained with dopa are cut on the freezing microtome without previous fixation.

Staining. All routine specimens, after having been cut on a rotary microtome into sections from 5 to 8 microns thick, are stained with hematoxylin and eosin. With this method, all nuclei stain blue, and collagen, muscle and nerves stain red. Special stains are employed for the demonstration of particular structures (see Table 1).

HISTOCHEMICAL STAINING

Brief mention may be made of two histochemical stains which have attained considerable practical importance: the Feulgen reaction and the Hotchkiss-McManus stain (DeLamater, Mescon and Barger). Both stains can be carried out on material fixed in 10 per cent Formalin.

The Feulgen reaction results in red staining of desoxyribonucleic acid (DNA) which is present in nuclei and in many virus inclusion bodies. On the other hand, ribonucleic acid (RNA), present in nucleoli, cytoplasm and keratohyalin, does not stain. This reaction is important as a stain for viruses since it often allows their differentiation from nucleoli and keratohyaline granules.

The Hotchkiss-McManus stain, or periodic acid-Schiff (PAS) stain, demonstrates the presence of polysaccharides, such as glycogen, hyaluronic acid and other mucoid substances, by staining them red. It is also of value in the study of fibrinoid degeneration where there is depolymerization of collagen resulting in the formation of polysaccharides. For the demonstration of glycogen, it is necessary to

compare two serial sections, one exposed to diastase prior to staining and the other not. Since the split products of glycogen resulting from the action of the diastase no longer are colored red by this stain, only such substances represent glycogen which stain red without preliminary diastase digestion but do not stain after diastase digestion.

In addition, the Hotchkiss-McManus stain is of great value in the demonstration of fungi. Since the cell walls of fungi are composed of a mixture of cellulose and chitin, they contain considerable amounts of polysaccharides. All fungi, therefore, stain bright red and thus are detected easily in histologic sections because other tissues stain very faintly or not at all (Kligman, Mescon and DeLamater).

POLARISCOPIC EXAMINATION

Polariscopic examination is the examination of histologic sections under the microscope with polarized light—i.e., with light from which all rays except those vibrating in one plane are excluded.

For the polariscopic examination, two disks made of polarizing plastics are inserted into the microscope. One disk is placed below the condenser of the microscope and acts as the polarizer. The second disk is placed into the eyepiece of the microscope and acts as the analyzer. When the eyepiece containing the analyzing disk is rotated so that the path of the light through the two disks is broken at a right angle, the field is dark. When, however, doubly refractile lipids are introduced between the two disks, they break the polarization and are visible as bright white bodies in the dark field.

Cholesterol and cholesterol esters are doubly refractile, while neutral fats are not. Doubly refractile fats are called anisotropic, the others isotropic. Doubly refractile lipids are present regularly in the cutaneous lesions of xanthomatosis and hyperlipemia, in xanthelasma palpebrarum and in extracellular cholesterosis. They are present occasionally in Hand-Schüller-Christian disease, in foreign-body granulomas and in histiocytoma. The lipid material in lipid proteinosis and necrobiosis lipoidica diabetorum, however, is not doubly refractile, as a rule.

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5

Morphology of the Mesodermal Cells

Various types of mesodermal cells infiltrate the dermis and occasionally the epidermis in the inflammatory dermatoses, in the granulomas and in the lymphomas. It is important for diagnostic purposes to identify the cell types. Three groups of mesodermal cells are recognized generally: the myeloid group, the lymphoid group and the reticular (or histiocytic) group. In addition, plasma cells and mast cells occur. It is likely that both originate from the reticular group of cells.

MYELOID GROUP

Polymorphonuclear leukocytes and eosinophilic leukocytes may occur in the skin in various dermatoses. Basophilic leukocytes, however, do not occur. In myelosis (myeloid leukemia), in addition to polymorphonuclear leukocytes and eosinophilic leukocytes, one finds immature myeloid cells—namely, myeloblasts and myelocytes.

Myeloblast and Myelocyte. The myeloblast is a large cell with non-granular cytoplasm and a round or oval, vesicular nucleus. The myelocyte differs from the myeloblast mainly by having in its cytoplasm either neutrophilic or eosinophilic granules. Myelocytes are always oxidase-positive, while myeloblasts may be oxidase-positive or oxidase-negative. (For a more detailed discussion, see page 494.)

Polymorphonuclear Leukocyte. The polymorphonuclear leukocyte, or neutrophil, has a lobated nucleus and contains fine neutrophilic granules in its cytoplasm. This cell occasionally is referred to as a microphage because it is a small phagocytic cell with the ability to phagocytize bacteria only. In contrast, the macrophage, a large phagocytic, histiocytic cell, also can take up particulate matter such as hemosiderin, melanin and lipid. Because of their ability to phagocytize bacteria, numerous polymorphonuclear leukocytes are present in the skin in acute bacterial infections, e.g., in erysipelas and folliculitis. In addition, they are found in conspicuous numbers in acute dermatitis, allergic vasculitis (anaphylactoid purpura), erythema

elevatum diutinum and the initial stages of erythema nodosum and nodular nonsuppurative panniculitis.

Eosinophilic Leukocyte. This cell, also called polymorphonuclear eosinophil, is characterized by the presence of coarse, round, brilliant eosinophilic granules in its cytoplasm. The granules are visible with routine stains but stand out more clearly when Giemsa's stain is used. Its nucleus is lobated and thus has the same appearance as that of the polymorphonuclear leukocyte. The cell is able to phagocytize bacteria. Polymorphonuclear eosinophils form as such in the bone marrow.

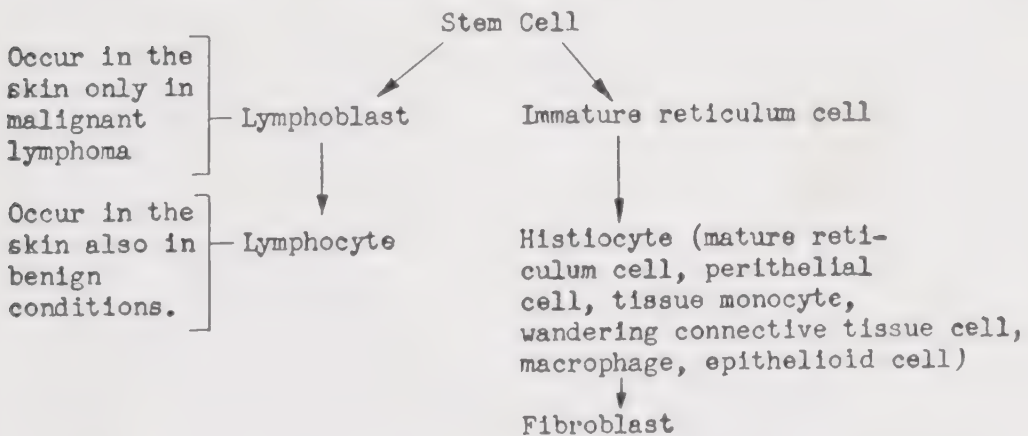
In addition to polymorphonuclear eosinophils, monolobed eosinophils are observed not infrequently in pathologic conditions of the skin (Burkhart and Montgomery). Their nuclei are either oval, kidney-shaped or band-shaped. It is possible that they represent histiocytic eosinophils and as such are formed in the skin.

Both the polymorphonuclear and the monolobed eosinophil occur in the tissue as a response to local anaphylaxis (Campbell). Tissue eosinophilia is apt to be prominent in eczematous drug eruptions, atopic dermatitis, dermatitis herpetiformis, pemphigus vegetans, allergic vasculitis (anaphylactoid purpura), eosinophilic granuloma, granuloma faciale, mycosis fungoides and Hodgkin's disease.

LYMPHOID GROUP

It is widely accepted that lymphoid and reticular cells arise from a common cell—the lymphoid-reticular stem cell (Chart 2).

CHART 2.—DEVELOPMENT OF LYMPHOID AND RETICULAR CELLS



Stem Cell. The stem cell can be seen in the skin only in highly malignant lymphomas. It is characterized by abundant, pale-staining cytoplasm and a large, round, pale nucleus containing delicate chro-

matin particles and one or two prominent nucleoli (see page 474 and Figure 260). This cell may develop into either a lymphoid cell (stem cell → lymphoblast → lymphocyte) or a reticular cell (stem cell → reticulum cell → histiocyte → fibroblast) (Gall and Mallory).

Lymphoblast. Lymphoblasts do not occur in ordinary inflammation of the skin but only in lymphoma. They are spherical cells and possess a large nucleus surrounded by a uniform, basophilic rim of cytoplasm. The nucleus is round or slightly indented (see page 477 and Figure 263). It is much larger and lighter than that of the mature lymphocyte.

Lymphocyte. Lymphocytes have much smaller nuclei and less cytoplasm than lymphoblasts. The nuclei are spherical and appear very darkly stained since the chromatin forms a thick layer at the periphery and several dark-staining particles in the interior.

Lymphocytes are found in the skin in most forms of lymphoma and in acute, subacute and chronic inflammations—for instance, in acute, subacute and chronic dermatitis, in psoriasis, in lichen planus and in lupus erythematosus. They also form a large proportion of the cells in most granulomas.

It is probable that the lymphocytes present in the skin are hematogenous in origin, except in malignant lymphoma, in which they may arise autochthonously. It is assumed by some authors that lymphocytes may transform into histiocytes (Kolouch). Some believe even that they may transform into fibroblasts (Goldsmith).

RETICULAR OR HISTIOCYTIC GROUP

The reticular or histiocytic group of cells belongs to the reticulo-endothelial system. The two outstanding properties of the reticular or histiocytic group of cells are their ability to absorb particulate matter and to produce reticulum fibers. As the cells age, they may change into fibroblasts (see Chart 2, page 33). As such, they no longer possess phagocytic powers and form collagen rather than reticulum.

No generally accepted nomenclature exists for the reticular group of cells. The following names are used by various authors as designation for the mature cell of this group: histiocyte, reticulum cell, clasmatocyte, perithelial cell, tissue monocyte and wandering connective-tissue cell. The term histiocyte at present is employed the most widely. Under special conditions, the histiocyte may become a macrophage or an epithelioid cell.

Immature cells of the reticular groups are observed in lymphoma and generally are referred to as reticulum cells. Therefore, lymphomas in which these cells predominate are called reticulum-cell

lymphoma. However, it should be kept in mind that many authors use the term reticulum cell also for mature reticular cells.

Reticulum Cell (Immature Reticular Cell). This cell, as seen in reticulum-cell lymphoma, possesses a nucleus which is smaller than that of a stem cell but larger than that of a histiocyte. The nucleus may be round but usually is oval or kidney-shaped. It is pale-staining and has a moderately heavy chromatin network and a distinct basophilic nuclear membrane (see page 474 and Figure 261). The cytoplasm is eosinophilic and abundant. It often is irregular in outline and may show pseudopodic protrusions. Because of their immaturity, the cells may form reticulum fibers only to a slight degree and have little or no phagocytic power.

Histiocyte (Mature Reticular Cell). Histiocytes are formed in the skin in contrast to lymphocytes which do not arise in the skin except in malignant lymphoma.

In the normal skin, histiocytes are present in small numbers around the capillaries ("perithelial cells"). Under pathologic conditions, which include the inflammatory diseases and the granulomas, histiocytes tend to wander from the pericapillary regions into the dermis ("tissue monocytes," "wandering connective-tissue cells").

Histiocytes are much smaller than reticulum cells but otherwise do not differ from them in appearance. Histiocytes form abundant reticulum fibers and possess the ability to phagocytize bacteria and particulate matter.

Histiocytes may resemble fibroblasts greatly and often it is not possible to state with certainty whether a given cell is a histiocyte or a fibroblast. As a rule, however, the nuclei of histiocytes are larger and stain slightly paler than those of fibroblasts. Although both may have oval nuclei, those of histiocytes tend to be kidney-shaped, those of fibroblasts spindle-shaped. While histiocytes possess the ability to form reticulum fibers, fibroblasts form collagen. It should be remembered that no sharp borderline exists between the histiocyte and the fibroblast, since the histiocyte presents the parent cell of the fibroblast and may develop into a fibroblast.

Macrophage. Histiocytes possess the ability to phagocytize particulate matter and certain micro-organisms. Those containing phagocytized material are called macrophages. Histiocytes migrate as wandering cells to areas where material digestible to them is present. They may ingest melanin and are then referred to as chromatophores or melanophores. They may ingest lipids and become foam cells. They may also ingest erythrocytes and hemosiderin as well as certain bacteria, fungi, viruses and protozoa. Examples of bacteria which may be ingested by histiocytes are lepra bacilli and Frisch bacilli; of

fungi, *Histoplasma capsulatum*; of viruses, Donovan bodies, and of protozoa, *Leishmania tropica*. When individual macrophages are unable to deal with particles to be removed, they tend to fuse together and to form multinucleated foreign-body giant cells. Excellent examples of foreign-body giant cells may be seen in paraffinoma, gout and Malherbe's calcifying epithelioma. The nuclei in foreign-body giant cells usually are clumped together in an irregular arrangement, but they may lie regularly along the periphery of the cell, so that foreign-body giant cells may be indistinguishable from Langhans giant cells.

Epithelioid Cell. Under certain conditions, histiocytes may change into epithelioid cells. Epithelioid cells possess a large, usually oval, pale, vesicular nucleus resembling the nucleus of epithelial cells and abundant, ill-defined, slightly eosinophilic cytoplasm. Pseudopodic elongations of the cytoplasm usually can be seen. When lying in groups, the cytoplasm of neighboring cells often appears coalesced. Epithelioid cells may form giant cells, the so-called Langhans type of giant cell. It is likely that this type of giant cell forms by amitotic nuclear division without cellular division. The nuclei are arranged in an arc along the periphery of the cell in horseshoe fashion. Epithelioid cells and Langhans giant cells have phagocytic power and have the ability to form reticulum fibers.

Epithelioid cells are found in a variety of granulomas, especially in tuberculosis, sarcoidosis, leprosy, syphilis, blastomycosis and coccidioidomycosis. In tuberculosis, epithelioid cells form as a tissue response to the lipid fraction of the tubercle bacillus (Sabin). As a granulomatous lesion containing epithelioid cells heals, the epithelioid cells may mature into fibroblasts and their reticulum fibers into collagenous fibers. This process can be observed particularly well in healing lesions of sarcoidosis.

Fibroblast. The common (resting) connective-tissue cells are called fibroblasts because they are instrumental in the elaboration of the collagenous fibers (see page 20). Their nuclei are elongated, often spindle-shaped. Because of their pale staining and the presence of a fine nuclear membrane, the nuclei have a vesicular appearance. The cell body, which is spindle-shaped, is not discerned easily. Fibroblasts usually are found adjacent to the surface of collagenous bundles.

PLASMA CELLS

The plasma cell has abundant cytoplasm which is deeply basophilic, homogeneous and sharply defined. The nucleus is eccentrically placed and round, and along its membrane shows coarse, dark-stain-

ing, regularly distributed chromatin particles. This gives the nucleus a cart-wheel appearance.

The origin of plasma cells from reticulum cells seems well established. All stages of transition between reticulum cells and plasma cells can be observed in the spleen of rabbits after repeated intravenous injections of horse serum. Antibodies are formed in great quantities in reticulum cells during their development into plasma cells, while mature plasma cells have already passed the stage of greatest activity (Fagraeus). It is assumed by some that not only reticulum cells but also all multipotent cells of the connective tissue as well as lymphocytes are capable of transforming into a plasma cell (Campbell and Good).

Plasma cells occur in small numbers in most chronic inflammatory diseases of the skin and in larger number in granulomas. They are particularly conspicuous in syphilis, granuloma inguinale and rhinoscleroma. In the presence of many plasma cells, but especially in rhinoscleroma, round, hyaline, acidophilic bodies, so-called Russell bodies, may be found within and outside of plasma cells. They form within plasma cells as a phenomenon of degeneration and finally are expelled (Pearse). They may attain a size twice that of a normal plasma cell. (See also page 202.)

MAST CELLS

Mast cells and basophilic leukocytes have nothing in common aside from an identical basophilic, metachromatic staining reaction of their granules. The mast cell is a histiocytic cell, the basophilic leukocyte a myeloid cell. Whereas mast cells are usually spindle-shaped and have an oval or round nucleus, basophilic leukocytes are round and have a lobated nucleus.

The granules of mast cells are soluble in ordinary fixatives such as Helly's and Zenker's fluids and do not stain with hematoxylin-eosin. Ten per cent Formalin, absolute alcohol and saturated basic lead acetate are suitable as fixatives and methylene blue or Giemsa's stain is suitable for staining the granules. The granules are basophilic (i.e., they stain with basic aniline dyes) and metachromatic (i.e., they may stain in a color different from that possessed by the dye). In this sense, the bluish dye thionine stains the mast-cell granules a reddish violet, toluidine blue stains them a purplish red and polychrome methylene blue stains them red (Michels).

Mast cells have two known functions, secretion of hyaluronic acid and secretion of heparin. That hyaluronic acid is present in the mast-cell granules is proved by the observations that mast-cell gran-

ules stain exactly like hyaluronic acid and no longer show metachromatic staining after the tissue containing them has been submitted to the action of hyaluronidase (Asboe-Hansen). Evidence for the presence of heparin in the mast-cell granules is: the similarity of reaction of the two substances to metachromatic staining and the parallelism existing between the amount of extractable heparin and the mast-cell content of certain organs (Jorpes).

Mast cells occur everywhere in the connective tissue of the body, particularly in the vicinity of capillaries and in the walls of larger blood vessels. The normal skin contains relatively few mast cells which are small and spindle-shaped. As a rule, they are arranged in groups around the blood vessels, but they occur also around the hair follicles and in the papillary layer of the dermis. Their number is increased in many different conditions (Asboe-Hansen). For instance, the granulation tissue in healing wounds contains more mast cells than normally are present. In most itching dermatoses, such as atopic eczema, contact dermatitis and lichen planus, an increased number of mast cells is present around the capillaries. In lupus erythematosus, in which there is an increase in the amount of hyaluronic acid in the dermis, the number of mast cells closely parallels the intensity of metachromatic staining. Also, neurofibromas and the stroma of carcinomas of the skin contain numerous mast cells. Thus, an increase in mast cells is of no diagnostic significance, except in urticaria pigmentosa where they occur in tumor-like aggregates, especially in the upper dermis.

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6

Congenital Diseases (Genodermatoses)

ICHTHYOSIS

Two forms of ichthyosis occur: *ichthyosis vulgaris* and *ichthyosis congenita*. In *ichthyosis vulgaris*, the skin is dry and rough and shows

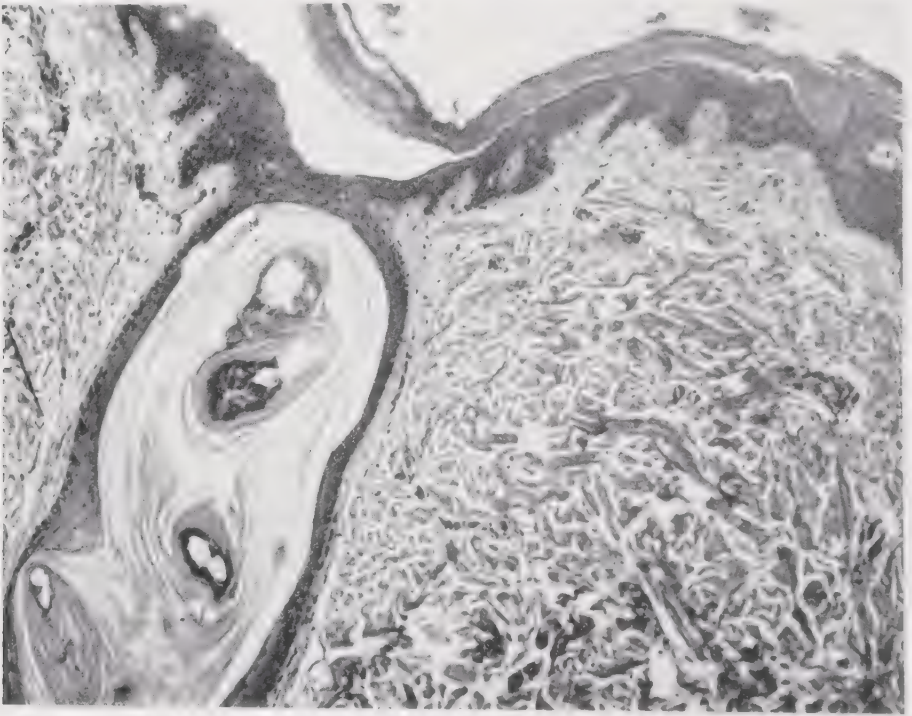


FIG. 12. *Ichthyosis vulgaris*. There are hyperkeratosis and absence of the granular layer. The stratum malpighii is thin, the rete ridges irregular. A large keratotic plug is located within a hair follicle. ($\times 100$)

scaling, often in the form of large lamellae resembling fish scales. Involvement is severest on the extensor surfaces of the extremities, while the flexures usually are spared. Follicular hyperkeratoses are frequently present.

Ichthyosis congenita is a more severe form of ichthyosis than

ichthyosis vulgaris. The skin is represented by a thick horny cuirass with development of deep fissures.

Ichthyosis hystrix is not related to ichthyosis but represents an extensive, or systematized, nevus verrucosus (see page 321).

Histopathology. The characteristic lesion of ichthyosis vulgaris is hyperkeratosis with diminution or even complete absence of the granular layer (Fig. 12). This represents an exception to the rule that an increase in thickness of the horny layer is accompanied by an increase in thickness also of the granular layer. The probable reason for this exceptional finding is that, in ichthyosis vulgaris, there is an inadequate shedding rather than an overproduction of horny cells. The hyperkeratosis in ichthyosis vulgaris is moderate and not associated with parakeratosis. The stratum malpighii is thinner than normal, and the rete ridges are diminished in number; some are atrophic while others are slender, elongated and branching (dove-tailed). The hyperkeratosis usually affects also the upper portion of the hair follicles, resulting in large, follicular, keratotic plugs. The pressure of the keratotic plugs causes atrophy of the lower portion of the follicles and of the sebaceous glands.

Ichthyosis congenita differs from ichthyosis vulgaris only by showing a much greater degree of hyperkeratosis. A stratum granulosum is usually present, but it is not prominent.

CONGENITAL ICHTHYOSIFORM ERYTHRODERMA

Like ichthyosis, this disease is characterized by dryness, roughness and scaling of the skin. In addition, generalized erythema is present and, in many cases, bullae occur. In contrast to ichthyosis, the flexural surfaces are involved most intensely.

Histopathology. In the erythematous areas of the skin, one observes pronounced hyperkeratosis with occasional islands of parakeratosis. A stratum granulosum is present. Although it varies in thickness, it is for the most part hypertrophic. The stratum malpighii shows acanthosis with irregular elongation of the rete ridges. The upper dermis shows a chronic inflammatory infiltrate.

Examination of bullous lesions has revealed in some cases merely presence of a nonspecific subcorneal bulla (MacKee and Rosen). In others, a pronounced ballooning of epidermal cells was noted either in the midportion of the epidermis (Ellis) or in the granular layer (Barker and Sachs). In the latter case, the changes in the granular layer resembled those seen in epidermodysplasia verruciformis. Ellis believes that the ballooning of epidermal cells is caused by a persistence of embryonal cells inasmuch as the cells of the embryonal stratum intermedium have a ballooned appearance (see page 4).

Differential Diagnosis. Congenital ichthyosiform erythroderma differs from ichthyosis by the presence of a usually hypertrophic granular layer, the presence of acanthosis and the presence of an inflammatory infiltrate in the dermis. In ichthyosis, the granular layer is diminished in thickness or absent, the stratum malpighii is thinner than normal and no infiltrate is present in the dermis (Layman and Murphy).

KERATOSIS PALMARIS ET PLANTARIS

This condition, which often is hereditary, is characterized by diffuse thickening of the horny layer of the palms and the soles. Because of the formation of fissures, the condition causes great discomfort to the patient.

Histopathology. The histologic picture is nonspecific, showing considerable hyperkeratosis as the only constant change. Occasionally there also are acanthosis and a chronic inflammatory infiltrate in the upper dermis.

KERATOSIS PUNCTATA PALMARIS ET PLANTARIS

Multiple, discrete, yellow to dark-brown, firm, slightly elevated, conical keratotic plugs, 1 to 3 mm. in diameter, are distributed symmetrically over the palms and the soles.

Histopathology. One observes a circumscribed hypertrophy of the stratum corneum consisting of a cone-shaped plug which invaginates the subjacent structures. Beneath this plug the stratum malpighii is thinned. The dermis is free of any inflammatory infiltrate (Scott, Costello and Simuango).

PACHYONYCHIA CONGENITA

This disease shows dystrophic changes of the nails, palmar and plantar hyperkeratosis, follicular keratosis and leukoplakia of the oral mucosa.

A variety of pachyonychia congenita is *dyskeratosis congenita*. It shares with pachyonychia congenita the dystrophic changes of the nails and the presence of leukoplakia. However, there are no hyperkeratotic changes of the skin. Instead, the skin shows atrophy and patches of hyperpigmentation.

Histopathology. In pachyonychia congenita, one observes hyperkeratosis with areas of parakeratosis. There is follicular plugging. Occasionally, horn plugs are present also in the sweat ducts (Andrews). The granular layer is hypertrophic. The stratum malpighii shows acanthosis with elongation of the rete ridges. A mild chronic inflammatory infiltrate is present in the upper dermis. Dyskeratotic

changes, similar to the corps ronds of Darier's disease, have been observed in the stratum malpighii of some cases (Andrews; Wright and Guequierre).

Dyskeratosis congenita shows thinning of the epidermis and almost complete absence of rete ridges. In areas in which the skin shows hyperpigmentation, the amount of melanin in the basal layer is increased and melanophores are present in the upper dermis (Cole, Rauschkolb and Toomey).

POROKERATOSIS MIBELLI

One or several lesions may be present. They show an atrophic center surrounded by a raised keratotic wall. The wall has on its top a groove filled with keratotic material.

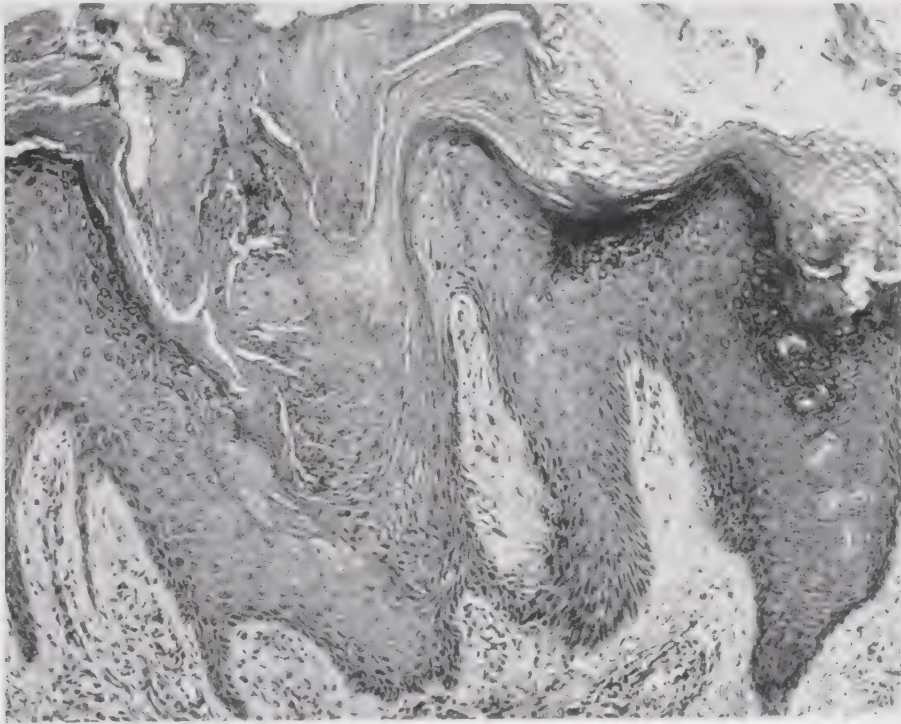


FIG. 13. Porokeratosis Mibelli. The section is taken from the keratotic wall. It shows the deep groove which forms the center of the keratotic wall. The groove is filled with a large horn plug, the "cornoid lamella." The cornoid lamella has a column of parakeratotic cells in its center. On the right is a normal sweat duct.

Histopathology. The atrophic center shows slight hyperkeratosis, atrophy of the stratum malpighii and fibrosis of the upper dermis. The keratotic wall shows considerable hyperkeratosis and acanthosis. In its center, the keratotic wall presents a deep groove filled by a large horn plug (the "cornoid lamella"). This cornoid lamella has

in its center a column of parakeratotic cells. Beneath the parakeratotic column, the granular layer is absent; elsewhere, it is well developed. The dermis underlying the cornoid lamella shows a chronic inflammatory infiltrate (Fig. 13).

Owing to the presence of the cornoid lamella, the histologic picture of porokeratosis is diagnostic. The name porokeratosis is a misnomer since the cornoid lamella is not necessarily located in the opening of a sweat duct.

XERODERMA PIGMENTOSUM

This disorder is associated with hypersensitivity to ultraviolet light. The lesions occur chiefly on exposed areas of the skin. An early and a late stage occur. In the early stage, one observes slight diffuse erythema with scaling and small areas of hyperpigmentation resembling freckles. In the late stage, atrophy of the skin, mottled pigmentation and telangiectases are present, giving the skin an appearance similar to that of chronic radiodermatitis. Warty growths appear within the atrophic skin, which may develop into carcinoma.

Histopathology. In the early stage, the histologic appearance is not always characteristic; the diagnosis often can be made from the combination of the histologic changes, however. There are: (1) hyperkeratosis, (2) thinning of the stratum malpighii with atrophy of some of the rete ridges and irregular proliferation and prolongation of others, (3) edema of the upper dermis, (4) a chronic inflammatory, predominantly perivascular infiltrate in the upper dermis and (5) spotted melanin pigmentation of the basal layer with melanophores in the upper dermis.

In the late stage, the epidermis shows atrophy in some areas and acanthosis in others. Atypical and multinucleated cells may be seen in the epidermis. The hyperkeratosis and hyperpigmentation already present in the early stage are more pronounced. The upper dermis shows degenerative changes of the collagen and of the elastic fibers of the same type as is seen in senile degeneration of the skin. Thus, one observes basophilic degeneration of the collagen and senile elastosis (see page 157). In some areas, the epidermis may show atypical downward growth so that the histologic picture in such areas is identical with that of senile keratosis.

Ultimately, squamous-cell carcinomas, and, occasionally, basal-cell epitheliomas and sarcomas develop in some of the lesions.

CONGENITAL ECTODERMAL DEFECT

This condition represents an incomplete development of the epidermis and its appendages. The skin is smooth and glossy. Hair

growth is sparse or completely absent. The facies is typical: it shows depressed nasal root and bridge, prominent frontal bosses and thick lips. In addition, there may be dental aplasia and dystrophy of the nails. Because of the diminution or the absence of sweat glands, the patient is unable to sweat adequately and therefore is intolerant to heat.

Histopathology. There is either a total absence of sweat glands or the presence of rudiments of nonfunctioning glands and ducts. There is usually a similar deficiency of pilosebaceous structures. The epidermis is thinner than normal and there may be likewise a reduction in the width of the dermis. The collagen, the elastic fibers and the blood vessels are normal in appearance, as a rule. Examination of the axillary skin in two cases revealed total absence of eccrine glands, while the apocrine glands were developed normally (Sunderman).

ROTHMUND'S SYNDROME, WERNER'S SYNDROME (PROGERIA OF ADULTS) AND PROGERIA OF CHILDREN

These are three different, though related, genodermatoses in which atrophy of the skin is a conspicuous feature.

Rothmund's syndrome, a familial disorder, starts in infancy with atrophy of the skin. Clinically, in addition to atrophy, the affected skin shows erythema, scaling, telangiectases and brownish pigmentation, so that the appearance of the skin resembles that of poikiloderma atrophicans vasculare. Cataracts develop in childhood.

Werner's syndrome (progeria of adults) is also familial but it does not start until the second or the third decade in life. The skin and also the subcutaneous fat and the musculature of the extremities undergo atrophy leading on the legs to ulcerations. Cataracts develop early in adult life.

Progeria of children is not familial. It starts several months after birth. The patient develops into a dwarf with a large skull and bird-like features. The skin appears atrophic and wrinkled.

Histopathology. No characteristic histologic features are seen in the skin in any of the three diseases. In all of them, the skin merely shows atrophy of the epidermis, thinning of the collagen bundles in the dermis and atrophy or even disappearance of the cutaneous appendages (Reed). The areas of erythema in Rothmund's syndrome, in spite of their clinical resemblance to poikiloderma atrophicans vasculare, show no inflammatory infiltrate but merely atrophy and telangiectasis (Thannhauser).

HYDROA VACCINIFORME AND HYDROA AESTIVALE

Hydroa is a recurring papulovesicular eruption occurring chiefly in the summer season, usually in boys, and solely on the exposed parts of the skin. Two forms exist: *hydroa aestivale*, the milder form, which does not produce scarring and ends at puberty, and *hydroa vacciniforme*, which produces scarring and persists as a rule through-

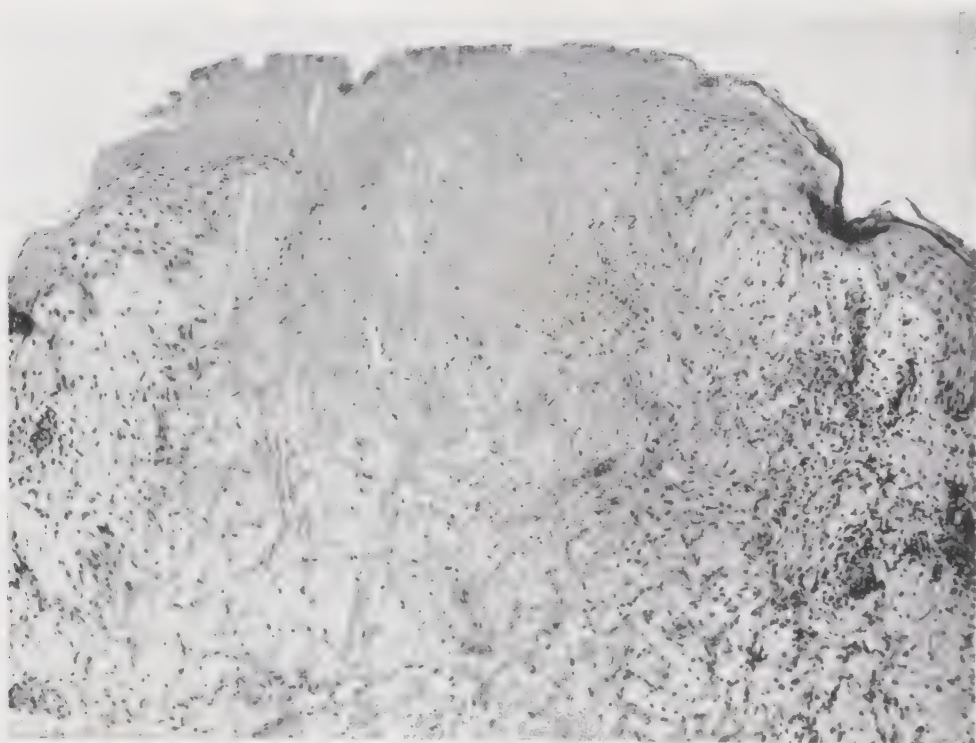


FIG. 14. *Hydroa vacciniforme*. There is a wedge-shaped area of necrosis involving the epidermis and the upper dermis. It is walled off by a chronic inflammatory infiltrate. ($\times 100$)

out life. In about one third of the cases, *hydroa vacciniforme* is associated with congenital porphyria, i.e., excretion of large amounts of uroporphyrin and coproporphyrin in the urine (see page 278).

Histopathology. In *hydroa vacciniforme*, a focal area of inflammation followed by necrosis forms in the upper dermis (Fig. 14). In the overlying epidermis, an intra-epidermal vesicle develops which at first is multilocular, but later, because of the degeneration of epithelial cells, becomes unilocular. The vesicle is filled with fibrin, leukocytes and the debris of epithelial cells. Within the area of necrosis located in the upper dermis, the blood vessels are thrombosed and foci of hemorrhage occur. The necrotic area is walled off with a chronic inflammatory infiltrate. On absorption of the necrotic area,

scarring results. In *hydroa aestivale*, the changes in the dermis are less severe than in *hydroa vacciniforme*. Therefore, healing takes place without scar formation.

EPIDERMOLYSIS BULLOSA

In this condition, vesicles or bullae form, usually at points of trauma but sometimes without trauma. Three forms of the disease exist: *epidermolysis bullosa simplex*, *epidermolysis bullosa dystrophica* and *epidermolysis bullosa hereditaria letalis*. The simple form is inherited dominantly, and the other two forms recessively. In the simple form, the bullae heal without scarring, the mucous membranes and the nails are rarely affected, and the disease improves or even subsides at puberty. In the dystrophic form, the lesions heal with atrophic scars, oral lesions and dystrophic changes of the nails are frequently present and the disease persists throughout life. In the third form, *epidermolysis bullosa hereditaria letalis*, death usually occurs within the first 3 months of life. The bullae show little tendency to heal but if they heal no scars remain. Oral lesions and dystrophic changes of the nails are usually present.

Histopathology. The bullae are always in subepidermal location in the dystrophic form (Tulipan) and in the lethal form (Lamb and Halpert; Schäffer); whereas in the simple form they may be found in subepidermal location (Leoni), in intra-epidermal or in subcorneal location (Johnson and Test). However, it is likely that also in *epidermolysis bullosa simplex* the bullae always form subepidermally; but, because of the tendency of the epidermis to rapid regeneration, the cleavage will be found intra-epidermally or subcorneally in bullae that are a few days old. (This occurs not infrequently in *erythema multiforme* and in *bullous pemphigoid*, see page 86.) No significant inflammatory reaction is observed in the dermis unless secondary infection has occurred. In the dystrophic form, small milium-like epidermal cysts may be found in the upper dermis (Tulipan).

Engman and Mook first described the absence of elastic fibers in the papillary and the subpapillary layers of involved as well as non-involved areas. They believed that the absence of elastic fibers was the cause of the disease. Although some authors have confirmed this finding, others have found the elastic tissue to be normal (Allen). In general, it appears that, in the simple form, the elastic tissue is normal (Johnson and Test), while, in the dystrophic form, the elastic tissue tends to be absent in the upper dermis of the involved areas (Tulipan; Lamb and Halpert). However, it is probable that the absence of elastic tissue in the dystrophic form is not primary but secondary and is the result of its destruction by the disease process. In

any case, recent studies of normal elastic tissue indicate that it plays no part in the coherence between epidermis and dermis (see page 8).

Differential Diagnosis. Differentiation of epidermolysis bullosa from other bullous diseases often is impossible. The presence of small epidermal cysts and the absence of elastic tissue, however, may aid in the establishment of the diagnosis.

DARIER'S DISEASE (KERATOSIS FOLLICULARIS)

This disease is characterized by a more or less extensive eruption consisting of hyperkeratotic or crusted papules which by confluence

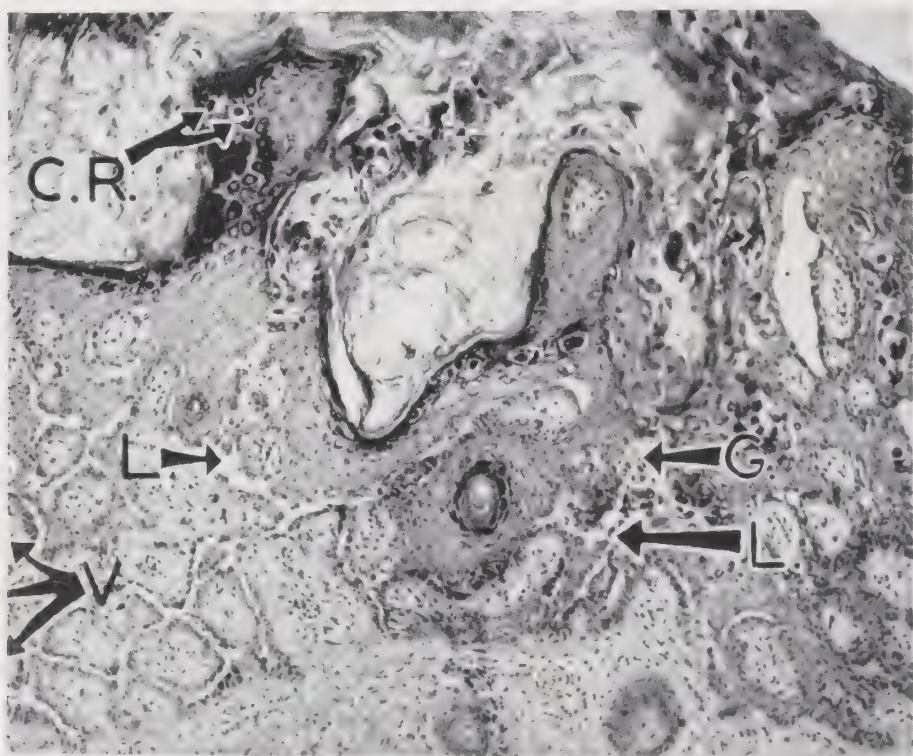


FIG. 15. Darier's disease. Low magnification. There are hyperkeratosis and papillomatosi. Numerous lacunae (L.) are present. On the left are elongated papilli lined by only one layer of cells, so-called villi (V.). Corps ronds (C.R.) are present in the granular layer, and grains (G.) in the horny layer and in some of the lacunae. ($\times 100$)

may form verrucous, crusted areas. Occasionally, hypertrophic lesions are present with elevated, verrucous formations. The oral mucosa is commonly, and the vulva, the larynx and the pharynx occasionally, involved (Brünauer).

Histopathology. The characteristic changes in Darier's disease are: (1) a peculiar form of dyskeratosis, namely, formation of corps ronds

and grains, (2) formation of lacunae and (3) irregular upward proliferation of papillae into the lacunae resulting in the formation of villi (Fig. 15). There also are papillomatosis, acanthosis and hyperkeratosis. The dermis shows a chronic inflammatory infiltrate. In

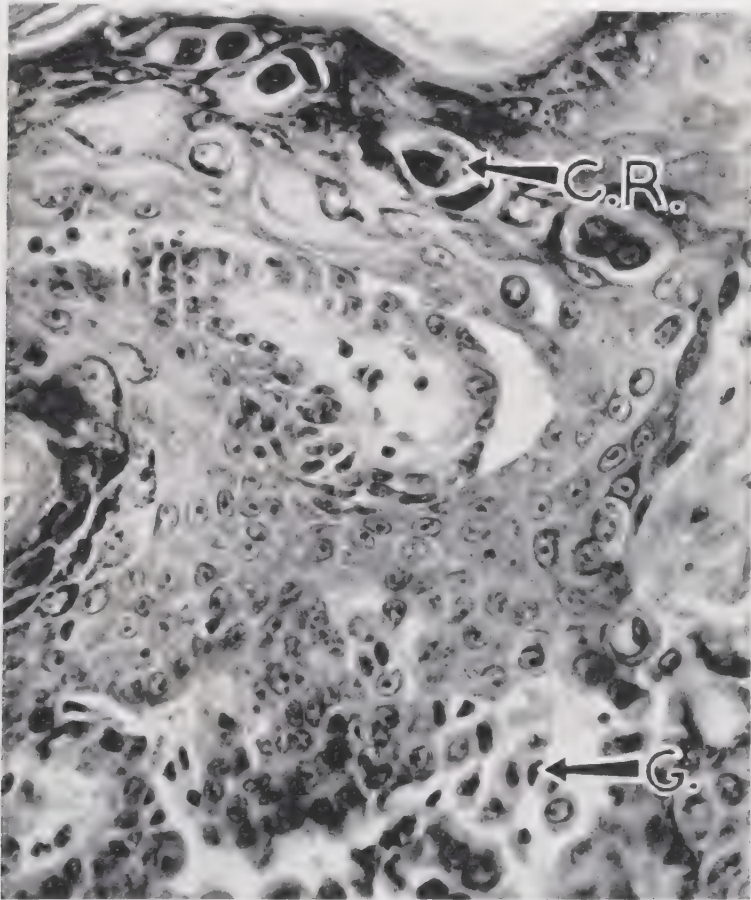


FIG. 16. Darier's disease. High magnification of Figure 15. In the upper third of the illustration, within the granular layer, are several corps ronds (C.R.), characterized by large, round, homogeneous, deep-staining nuclei. In the lower third, within a lacuna, are grains (G.), characterized by small, often grain-shaped nuclei. ($\times 400$)

some cases, in addition, there is downward proliferation of epidermal cells into the dermis.

The corps ronds occur mainly in the stratum malpighii and the granular layer, while the grains occur mainly in the horny layer. Both may be found within the lacunae. Corps ronds possess large, round, homogeneous, deeply basophilic nuclei and a homogeneous (hyalinized), deeply eosinophilic cytoplasm lined by a distinct membrane. They are much larger than normal squamous cells (Fig. 16). Corps

ronds develop on account of premature partial keratinization of the cell prior to reaching the horny layer, a process called benign dyskeratosis. (Malignant dyskeratosis is observed in Bowen's disease and in squamous-cell carcinoma.)

The grains are small cells, considerably smaller than the corps ronds. They resemble parakeratotic cells except that their nuclei are more prominent. The nuclei are elongated, often grain-shaped.

The lacunae represent small, slitlike, intra-epidermal vesicles which are found most commonly directly above the basal layer. They contain desquamated, acantholytic epidermal cells which have lost their intercellular bridges due either to degenerative changes or to partial keratinization. Corps ronds and, especially, grains are present among these desquamated cells.

Elongated, often tortuous papillae lined usually with but a single layer of basal cells project into the lacunae. They often are referred to as villi.

The hyperkeratosis and the papillomatosis cause the formation of keratotic plugs. They often fill the pilosebaceous follicles but also are found outside of follicles. Darier's disease, therefore, is not, as Darier originally thought, primarily a follicular disease. Proof of this is the fact that areas devoid of follicles, such as palms, soles and oral mucosa, may be affected (Ellis). The term *keratosis follicularis* is, then, a misnomer.

In some cases of Darier's disease, but especially in those with hypertrophic lesions, one observes considerable downward proliferation of the epidermis, either as a proliferation of basal cells or as pseudo-epitheliomatous hyperplasia (Beerman). The proliferations of basal cells consist of long, narrow cords composed of two rows of basal cells between which there may or may not be a lacunar space. These proliferations may send out branches and may penetrate deep into the dermis. The pseudo-epitheliomatous hyperplasia may suggest squamous-cell carcinoma, but, so far, no case of Darier's disease resulting in malignancy has been reported. (For a discussion of pseudo-epitheliomatous hyperplasia, see page 334.)

The lesions on the oral and other mucous membranes are analogous to those observed on the skin, except that hyperkeratotic changes are mild or absent (Brünauer).

Differential Diagnosis. For the differentiation of Darier's disease from familial benign chronic pemphigus, see below. The villous proliferations into the lacunar spaces may resemble those of syringo-cystadenoma papilliferum (Beerman). However, in the latter condi-

tion, two rows of epithelial cells line the villi. Furthermore, no dyskeratosis occurs and large apocrine glands are present in the dermis.

FAMILIAL BENIGN CHRONIC PEMPHIGUS

(Hailey and Hailey)

This disease (which often, but not always, is familial) is characterized by a localized recurrent eruption of vesicles and bullae. By peripheral extension, the lesions may assume a circinate configuration.

Histopathology. Although early lesions may show, like Darier's disease, small suprabasal separations, so-called lacunae, fully devel-

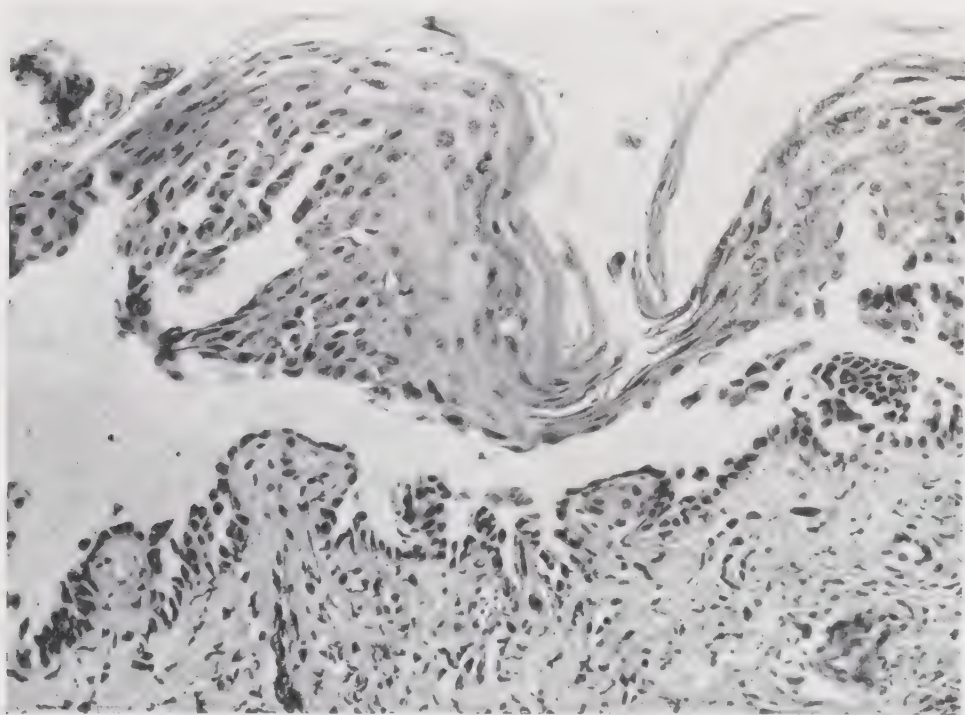
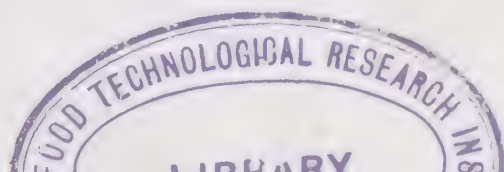


FIG. 17. Familial benign chronic pemphigus (Hailey and Hailey). The bulla is suprabasal in position. One observes loss of intercellular bridges, resulting in considerable acantholysis, and formation of villi (upward growth of papillae). These features cause a surprising resemblance to the bulla of pemphigus vulgaris. ($\times 200$)

oped lesions show large separations, namely bullae in suprabasal position (Fig. 17). Villi, i.e., elongated papillae lined by a single layer of basal cells, protrude upward into the bullae and, in some cases, cords of basal cells proliferate downward into the dermis. The bullae con-



tain acantholytic cells some of which show evidence of keratinization. Occasionally, there is evidence of dyskeratosis; namely, shrinking of some of the acantholytic cells which then assume the appearance of grains. However, corps ronds have been described in only a few cases (Ellis; Winer and Leeb).

Differential Diagnosis. Familial benign chronic pemphigus shares certain histologic features with both Darier's disease and pemphigus vulgaris. In all three diseases, one finds suprabasal separations of the epidermis caused by acantholysis and upward proliferation of papillae as so-called villi into the resulting lacunae or bullae. Familial benign chronic pemphigus, however, differs from Darier's disease by the larger size of the suprabasal separations (which thus appear as bullae rather than as lacunae), and the lesser degree or even the absence of dyskeratosis. If dyskeratosis is absent, differentiation from pemphigus vulgaris may be impossible. Occasionally, however, one observes in familial benign chronic pemphigus, even in the absence of dyskeratosis, an early onset of keratinization in the lower layers of the detached epidermis. The presence of eosinophils in the bullae points toward a diagnosis of pemphigus vulgaris, but their absence does not rule it out.

The nosologic position of the disease is at present uncertain. The presence of dyskeratotic changes in most cases of familial benign chronic pemphigus has led some observers to regard this disease as a bullous variant of Darier's disease (Ellis; Finnerud and Szymanski; Winer and Leeb). However, until more is known about the cause of the disease, it may be best to regard it as an independent entity (Hailey and Hailey; Frank and Rein).

EPIDERMODYSPLASIA VERRUCIFORMIS

(Lewandowsky and Lutz)

In this dermatosis, one finds an extensive eruption of flat-topped hyperkeratotic lesions resembling verrucae planae. By confluence, lichenified plaques may form.

Histopathology. The histologic changes consist of hyperkeratosis, increase in the thickness of the granular layer, acanthosis and a peculiar vacuolization of the cells in the upper layers of the stratum malpighii, of the granular cells and of the horny cells. Because of the vacuolization, the horny layer shows a loosely felted, basket-weave pattern. The histologic picture is like that of verruca plana (Fig. 122) with two exceptions: (1) in epidermodysplasia verruciformis, the nuclei of the vacuolated cells show more pronounced pyknosis and fragmentation than in verruca plana (Sullivan and Ellis; Waisman and Montgomery) and (2) the lesions change oc-

casionally into basal-cell epithelioma (Sullivan and Ellis) or squamous-cell carcinoma (Costa and Junqueira; Ormea).

In 1946, Lutz (one of the original describers), on the basis of successful implantation tests, stated that epidermodysplasia is "not an independent dermatosis, but rather a generalized eruption of warts with somewhat peculiar characteristics." Yet, some authors, though conceding that Lutz' case was one of verrucae planae, still regard epidermodysplasia verruciformis as an entity (Ormea; Teodorescu; Midana). Midana obtained negative results in auto-inoculation experiments performed on two patients. Teodorescu found in two patients, associated with the epidermodysplasia verruciformis, keratosis palmaris et plantaris hereditaria and regarded both diseases as genodermatoses.

ACROKERATOSIS VERRUCIFORMIS

(Hopf)

Numerous hyperkeratotic and occasionally verrucous papules are present, predominantly on the dorsa of the hands and the feet.

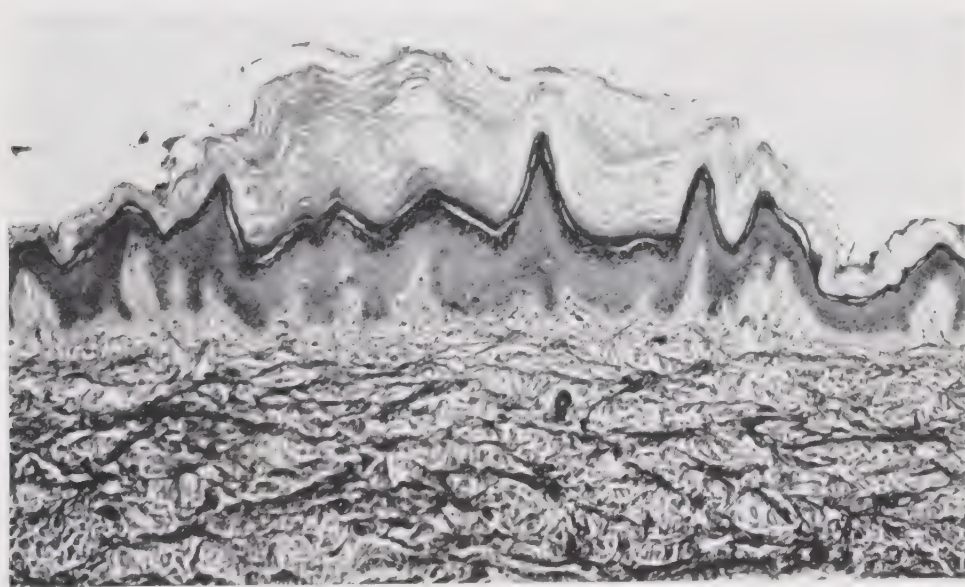


FIG. 18. Acrokeratosis verruciformis (Hopf). The lesion consists of a circumscribed area of papillomatosis, acanthosis and hyperkeratosis. ($\times 100$)

Histopathology. The papules show considerable hyperkeratosis, increase in thickness of the granular layer and acanthosis (Fig. 18). In addition, there are slight papillomatosis and some thickening of the rete ridges. The rete ridges all extend to a uniform level and their configuration is well preserved. There is no parakeratosis or

vacuolization of cells such as is seen in verruca vulgaris and verruca plana (Loveman; Niedelman).

PSEUDOXANTHOMA ELASTICUM

This disorder represents a congenital defect of the elastic tissue which may be limited in extent or widespread. In addition to the elastic tissue in the dermis, the elastic membrane of the retina, called

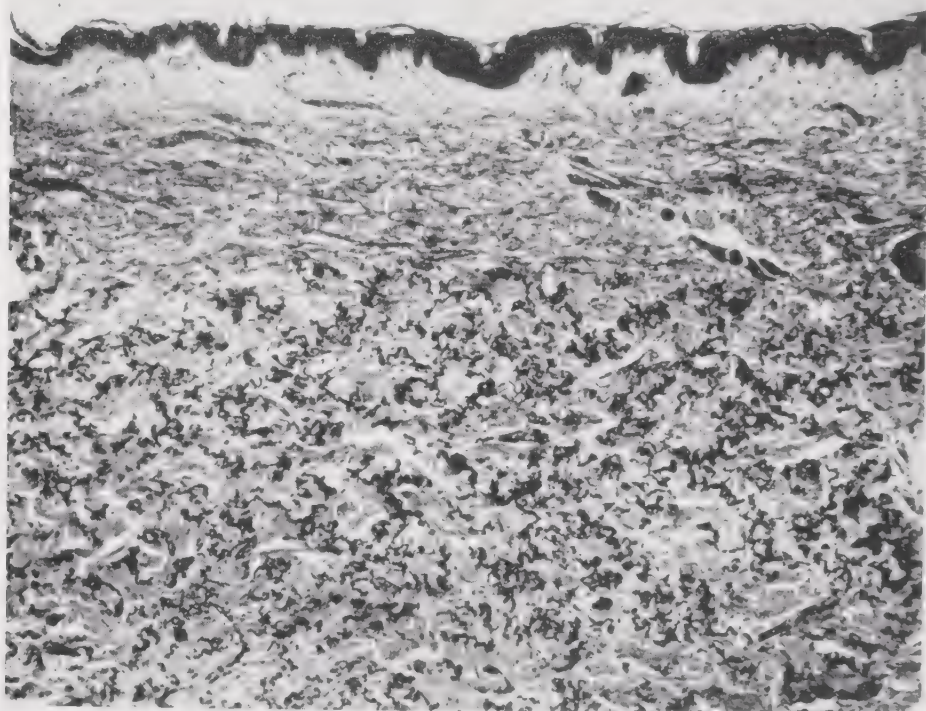


FIG. 19. *Pseudoxanthoma elasticum*. Low magnification, Verhoeff stain. This illustration shows the usually observed late degenerative stage. In the lower dermis, the elastic fibers are increased in number, appear swollen and show signs of degeneration, such as fragmentation, disintegration and clumping. (Patient's age, 31 years.) ($\times 50$)

Bruch's membrane, and the elastic fibers in the aorta, the arteries and the arterioles may be affected. The degeneration of the elastic fibers of Bruch's membrane causes small defects and breaks which manifest themselves clinically as angioid streaks (Urbach and Wolfram; Hagedoorn; Ebert). Involvement of the aorta causes diffuse dilatation (Urbach).

The cutaneous lesions consist of soft, yellowish papules and plaques. The papules frequently show a linear arrangement. The sides of the neck are the most common site of the lesions.

Histopathology. Histologic examination of the skin reveals the elastic tissue to be normal in the subepidermal portion of the dermis

In the middle and lower portions of the dermis, however, it is increased, usually in circumscribed areas. Within these areas, the elastic fibers are swollen and show degenerative changes such as fragmentation, disintegration and clumping (Figs. 19, 20). Because of degeneration and imbibition with calcium, the elastic fibers may assume a basophilic staining and become visible with routine stains. Fin-

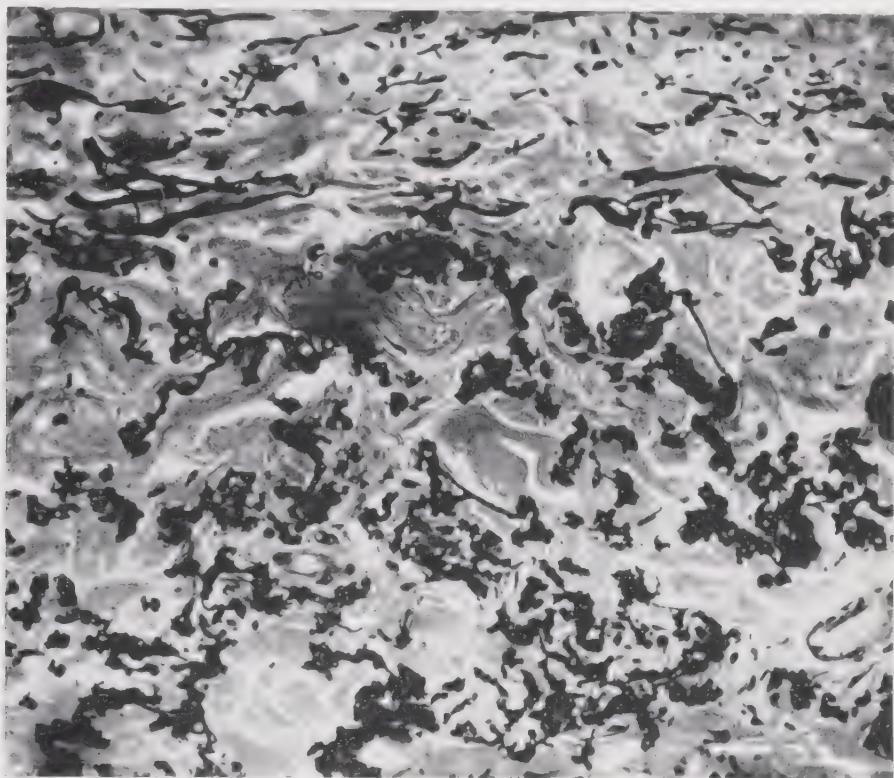


FIG. 20. *Pseudoxanthoma elasticum*. High magnification of Figure 19, Verhoeff stain. The elastic fibers are degenerated, whereas the collagen shows no evidence of degeneration. ($\times 200$)

nerud and Nomland have shown by staining methods (von Kossa's stain for calcium) and Lobitz and Osterberg by micro-incineration that the degenerated elastic fibers are richly infiltrated with calcium. The collagen fibers are unaltered.

In a few instances, the elastic tissue of the arterioles and the small arteries in the deep dermis was found to have undergone a similar degeneration (Urbach; de Sá Penella and Esteves).

It appears that pseudoxanthoma elasticum occasionally is preceded by an early hyperplastic stage (Fig. 21). In this stage, which seems to be present only during infancy and childhood, the elastic fibers are increased in number and size but show no evidence of degeneration

as they do in the more commonly observed late degenerative stage (Weidman, Anderson and Ayres; Pautrier).

Differential Diagnosis. Senile elastosis, like pseudoxanthoma elasticum, shows a great increase in material taking the elastic tissue stain. However, in senile elastosis this material is located in the upper third

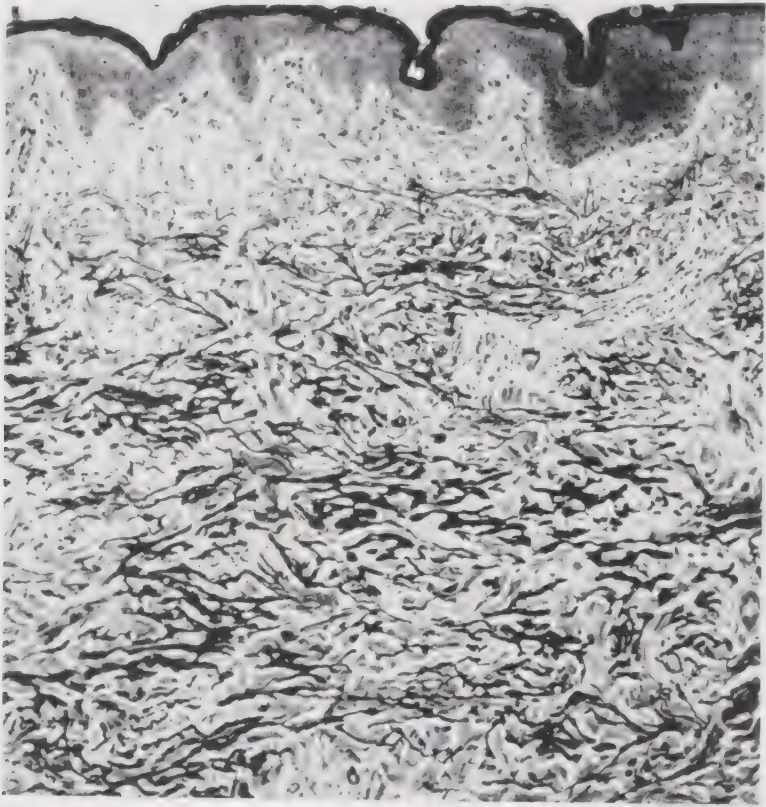


FIG. 21. *Pseudoxanthoma elasticum*. Low magnification, Verhoeff stain. This illustration shows the early hyperplastic stage. The elastic fibers are large and swollen but show no evidence of degeneration. (Patient's age, 2 years.) ($\times 100$)

of the dermis and is present as dense masses rather than as individual curls. Furthermore, staining of this material for calcium is always negative in senile elastosis.

CUTIS HYPERELASTICA (EHLERS-DANLOS SYNDROME)

This syndrome consists of (1) hyperelasticity of the skin, (2) hyperextensibility of the joints, (3) fragility of the skin and the blood vessels with formation of atrophic scars and (4) development of raisin-like pseudotumors. The pseudotumors form at points of trauma and are soft and pigmented and present a wrinkled surface.

In many cases small, hard, subcutaneous nodules have been described. They also are the result of trauma.

Histopathology. Degenerative changes are observed in both the collagenous and the elastic tissue. Many authors feel that the changes in the collagen are primary and predominant (Korting and Gottron). The collagen bundles appear atrophic, split up and separated by edema. The elastic fibers are normal in some cases but in most cases show breaking up and clumping. The amount of elastic tissue often appears increased; but it is likely that this increase is not a real one but is simulated by the atrophy of the collagen. In addition, the number of capillaries is increased and their lumina dilated. Large, round cystic spaces representing lymphangiectatic cavities may occur (Korting and Gottron).

The raisinlike pseudotumors that are part of the syndrome form at areas of traumatic hemorrhage and consist either of accumulations of foreign-body giant cells (Ronchese) or of proliferated connective tissue with large numbers of vessels in it. The hard subcutaneous nodules contain calcified necrotic fat or mucoid material enclosed in a thick fibrous capsule (Johnson and Falls).

URTICARIA PIGMENTOSA

This disorder is characterized in most cases by the presence of a great number of brown macules scattered over the entire cutaneous surface. When rubbed with a blunt instrument, they become distinctly urticarial. In rare instances, the lesions consist of one or several soft nodules or plaques.

Histopathology. The histologic picture shows an infiltrate composed chiefly of mast cells. Mast cells are characterized by the presence of basophilic, metachromatic granules in their cytoplasm (see pages 37, 38). These granules are not visible on staining with routine stains. Their demonstration requires special staining (see pages 28, 29 and Plate 1). Fixation in 10 per cent Formalin (without subsequent exposure to Helly's solution) and staining with Giemsa's stain or with methylene blue are recommended.

In the macular type, mast cells are present in the upper third of the dermis, especially around the capillaries. Some appear to be round or oval, but the majority are spindle-shaped. Since in sections stained with hematoxylin and eosin the mast cells resemble fibroblasts, the diagnosis may be missed easily unless special staining is employed.

In the nodular type (Figs. 22, 23), mast cells lie closely packed in tumorlike aggregates. The infiltrate may extend through the entire dermis into the subcutis. Wherever the mast cells lie in dense aggregates, they are cuboidal rather than spindle-shaped and show ample, slightly eosinophilic cytoplasm. Because of their shape and ample

cytoplasm, they look unlike any other cell and the diagnosis can be made without resorting to special staining.

If a biopsy is performed shortly after the lesion has been stroked, the section will show edema, an influx of eosinophils and shrinking of the mast cells associated with a great decrease in the amount of

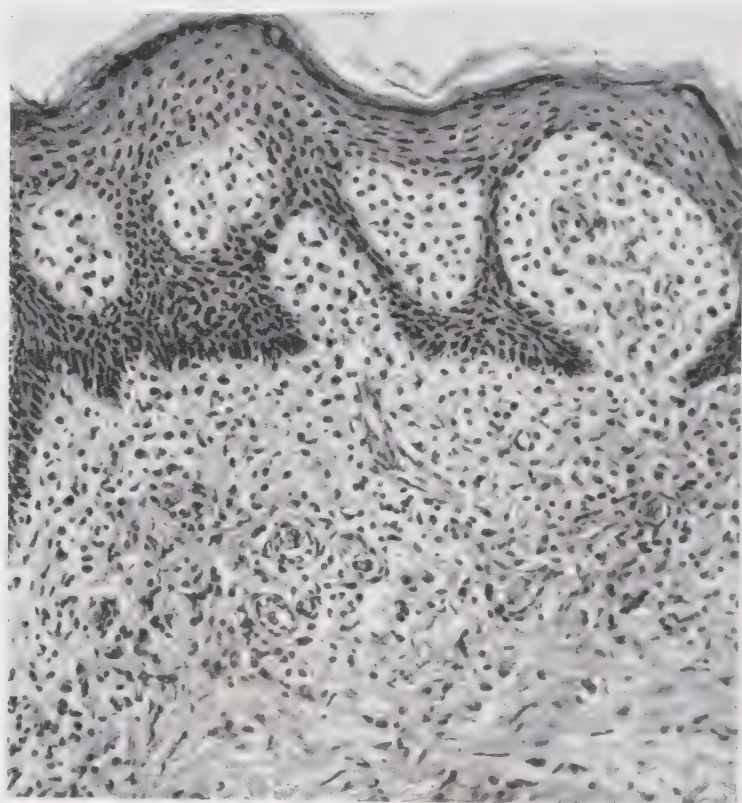


FIG. 22. Urticaria pigmentosa, nodular type. Low magnification, hematoxylin-eosin stain. Mast cells lie closely packed in the upper dermis. They are cuboidal in shape. Because of staining with hematoxylin-eosin, the granules in the mast cells are not visible. ($\times 200$)

granules within them, indicating that the granules have been expelled from the cells (Drennan). There may even be disintegration and a temporary disappearance of mast cells which may be the explanation for certain reports in the literature where in otherwise typical cases of urticaria pigmentosa mast cells have not been found (Drennan and Beare).

The pigmentation of urticaria pigmentosa is due not to the presence of the mast cells but to melanin, which is present in increased amounts in the basal layer and occasionally also in melanophores.

The presence of extracutaneous lesions in urticaria pigmentosa has been reported recently. However, the systemic lesions in Ellis'

case may well have been lymphoma; and the bone lesions in Sagher's and Clyman's cases were not examined histologically.

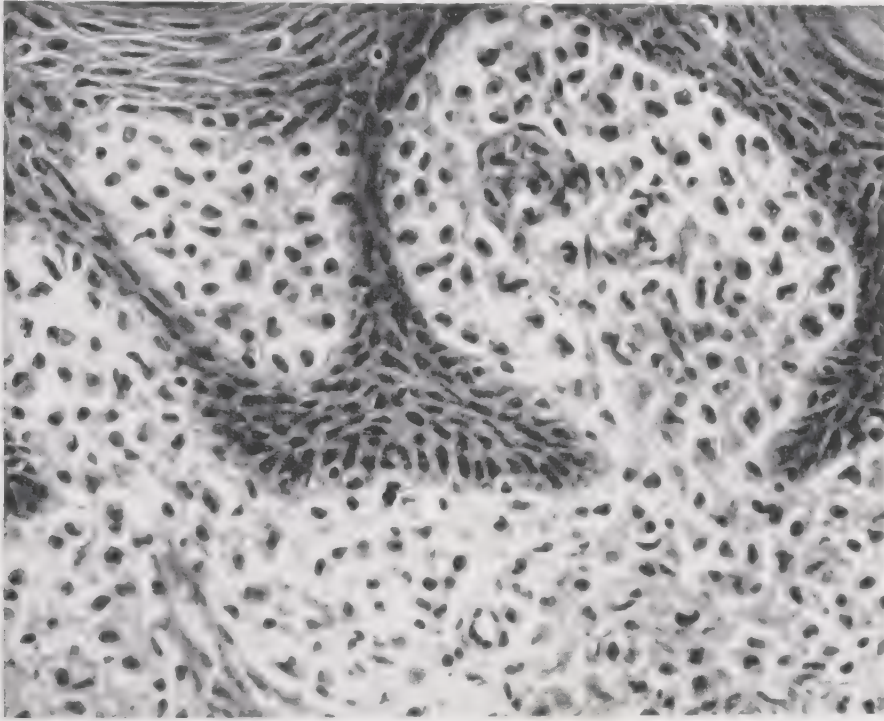


FIG. 23. Urticaria pigmentosa, nodular type. High magnification of Figure 22, hematoxylin-eosin stain. The mast cells appear as large, cuboidal cells. ($\times 400$)

INCONTINENTIA PIGMENTI

The disease frequently begins immediately after birth with inflammatory lesions, particularly bullae, in linear and grouped arrangement. The bullae may recur for months. They finally give way to areas of pigmentation. There may be an intermediary stage of linear, verrucous lesions. The pigmented areas are widely disseminated, located especially on the trunk, and have an irregular, bizarre outline.

Histopathology. In the early vesicular stage, one observes intra-epidermally located vesicles containing many eosinophils (Carney; Epstein, Vedder and Pinkus). In addition, there is spongiosis of the epidermis, and in the dermis an infiltrate composed of lymphocytes, eosinophils and neutrophils.

The intermediary stage shows hyperkeratosis, acanthosis and a non-specific inflammatory infiltrate.

The final stage shows diminution or absence of melanin in the basal layer of the epidermis and extensive deposits of melanin inside

and outside of melanophores in the upper dermis. In many cases, the basal cells show degeneration and vacuolization. It is believed generally that the disease causes damage to the cells in the basal layer so that the melanocytes become incapable of holding and metabolizing melanin (Sulzberger; Doornink).

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7

Noninfectious Vesicular and Bullous Diseases

Several new concepts have been introduced in recent years concerning the histologic structure of vesicles and bullae and their mechanism of formation. It appears appropriate, therefore, to present a classification of the different types of vesicles and bullae and to outline briefly their mode of formation before discussing individual diseases. (Since, from a histologic point of view, it is immaterial whether a lesion is a vesicle or a bulla, only the latter term will be used in the following presentation.)

Eight distinct types of bullae can be recognized (Table 2).

1. *Subcorneal bulla*. Detachment of the horny layer from the stratum malpighii occurs.

2. *Spongiotic bulla*. Liquefaction necrosis of a few epidermal cells causes formation of a minute cavity (*vésiculette primordiale*) which subsequently, due to intercellular edema (spongiosis) and intracellular edema (*altération cavitaire*) in the surrounding epidermis, enlarges into an intra-epidermal bulla. In the case of pronounced intracellular edema, reticular degeneration of the epidermis may occur. (For a detailed description, see page 69.)

3. *Miliarial bulla*. In miliaria, bullae form due to the escape of sweat from the sweat ducts. Two types occur: miliaria crystallina, in which the bulla is located within the stratum corneum, and miliaria rubra, in which the bulla forms either within the stratum malpighii or beneath the epidermis. In severe cases of miliaria rubra, the sweat duct ruptures. (For a detailed description, see page 76.)

4. *Acantholytic bulla*. Degeneration of intercellular bridges causes loss of coherence between epidermal cells and formation of rifts which enlarge into bullae. Detached (acantholytic) epidermal cells are present in the bulla cavity. Acantholysis may take place within the lower epidermis, predominantly right above the basal layer, or within the upper epidermis, predominantly within the granular layer. (For a detailed description, see pages 77 and 82.)

TABLE 2.—CLASSIFICATION OF VESICLES AND BULLAE

TYPE OF VESICLE OR BULLA	MODE OF FORMATION	SITE OF FORMATION	DISEASES
1. Subcorneal bulla	Detachment of horny layer	Subcorneal	Impetigo
2. Spongiotic bulla	Cellular necrosis fol- lowed by spongiosis and, occasionally, by reticular degen- eration	Intra-epidermal	Dermatitis-Eczema Pompholyx Congenital ichthyosiform erythroderma Hydroa
3. Miliarial bulla	Retention of sweat	Intracorneal Intra-epidermal or subepidermal	Miliaria crystallina Miliaria rubra
4. Acantholytic bulla	Acantholysis	Intra-epidermal a. suprabasal	Pemphigus vulgaris Pemphigus vegetans Familial benign chronic pemphigus Darier's disease Senile keratosis
		b. upper epi- dermis	Pemphigus foliaceus Pemphigus erythematosus
5. Viral bulla	Reticular and balloon- ing degeneration with acantholysis	Intra-epidermal	Variola Herpes simplex Herpes zoster Varicella
6. Pressure bulla	Detachment of entire epidermis	Subepidermal	Bullous pemphigoid Benign mucous-mem- brane pemphigoid Dermatitis herpetiformis Erythema multiforme Epidermolysis bullosa Porphyria cutanea tarda
7. Bulla due to basal- cell degeneration	Degeneration of basal cells	Subepidermal	Incontinentia pigmenti Lichen planus Lichen sclerosus et atrophicus Lupus erythematosus
8. Bulla due to reticu- lum degeneration	Degeneration of sub- epidermal reticulum fibers	Subepidermal	Burns

5. *Viral bulla*. Invasion of epidermal cells by certain viruses causes two types of degenerative changes in epidermal cells: ballooning and reticular degeneration. Ballooning degeneration leads to extensive acantholysis. Although the bullae form within the epidermis, progression of the ballooning degeneration leads to a subepidermal location in older bullae. (For a detailed description, see page 239.)

6. *Pressure bulla*. Detachment of the entire epidermis from the dermis occurs. Pressure of the accumulating tissue fluid often causes in early bullae rounding of the lateral walls and stretching of the epidermal cells located there. Older bullae, due to regeneration of the epidermis at the floor of the bulla, may have an intra-epidermal location. If, in addition, disintegration of the detached stratum malpighii occurs, the bulla may be subcorneal in location. (For a detailed description, see page 86.)

7. *Bulla due to basal-cell degeneration*. Several diseases (see Table 2) cause hydropic degeneration of the basal cells. This may result in damage to the cytoplasmic processes which effect the coherence of the basal-cell layer with the dermis. Thus, a subepidermal bulla may form. (For a detailed description, see page 296.)

8. *Bulla due to reticulum degeneration*. Damage to the subepidermal feltwork of reticulum fibers causes the cytoplasmic processes of basal cells to pull out of this feltwork. A subepidermal bulla forms into which numerous cytoplasmic processes extend from the basal cells at the roof of the bulla. (For a detailed description, see page 90.)

DERMATITIS-ECZEMA

The terms dermatitis and eczema now are used generally as synonyms. They refer to an inflammation of the skin, based on an allergic response of the skin to a variety of agents, such as chemicals, proteins, bacteria and fungi. The exciting allergen may act on the skin either from the outside or from the inside.

Dermatitis, or eczema, may be acute, subacute or chronic. The clinical picture is characterized by polymorphism of the eruption. Among the primary lesions that may be observed are macules, papules and vesicles; the macules and papules tend to coalesce to form areas of diffuse erythema. Among the secondary lesions are scaling, crusting, lichenification and fissuring. The lesions of dermatitis usually are not demarcated sharply but merge gradually into the surrounding normal skin. Moderately severe to severe itching is present in most forms of dermatitis.

No generally accepted classification of dermatitis exists and many cases defy assignment to any definite type. In this section, the following types of dermatitis will be discussed: (1) contact dermatitis;

(2) nummular eczema; (3) atopic dermatitis (or neurodermatitis disseminata); (4) lichen simplex chronicus (or neurodermatitis circumscripta); (5) exudative discoid and lichenoid chronic dermatosis; (6) seborrheic dermatitis, including Leiner's disease; (7) stasis dermatitis and (8) generalized exfoliative dermatitis. In addition, lesions of dermatitis may occur in superficial fungus infections, as drug eruptions and in lymphoma. The latter three forms of dermatitis will be discussed when the respective diseases are described.

Contact dermatitis is caused by contact of the skin with an agent that acts either as a specific allergic sensitizer or as a primary irritant. Contact dermatitis may be acute, subacute or chronic. In acute and subacute contact dermatitis, diffuse erythema, edema, oozing and crusting predominate; in addition, vesicles are often present if a specific allergic sensitizer is the cause. In chronic contact dermatitis, erythema, scaling and lichenification prevail.

Nummular eczema, probably caused by a temporary loss of resistance in the skin to the ordinary bacterial flora of the skin, presents fairly sharply demarcated patches of erythema studded with discrete "pinpoint vesicles" or "pinpoint erosions."

Atopic dermatitis, a constitutional, familial dermatosis of unknown cause, which often is aggravated by emotional tension or allergic factors, shows lichenified and scaling erythematous areas, which, when active, show also oozing and crusting but no vesicles.

Lichen simplex chronicus shows one or several lichenified plaques with little scaling. Oozing and vesiculation are absent. On the lower legs especially, lichen simplex chronicus may become hypertrophic and assume a verrucous, nodular appearance (lichenificatio gigantea, lichen corneus hypertrophicus).

Exudative discoid and lichenoid chronic dermatosis shows patchy lesions which in their early stages show vesicles, oozing and crusting, and later lichenification and scaling. It is likely that it does not represent an entity but a variant of nummular eczema.

Seborrheic dermatitis shows fairly sharply demarcated, brownish red areas which show only little infiltration and are covered with fine, greasy scales. Oozing may be present but no vesiculation is found. Generalized seborrheic dermatitis in infants often is referred to as Leiner's disease.

Stasis dermatitis presents erythema, edema, scaling and occasionally oozing and crusting. It differs from other forms of dermatitis, first, by showing brownish pigmentation due to hemosiderin deposits and, second, by resulting, in some instances, in ulceration and atrophy.

Generalized exfoliative dermatitis shows involvement of the entire skin with erythema, edema, abundant scaling and, in severe cases,

oozing. It represents a peak reaction to which several forms of dermatitis may lead—for instance, contact dermatitis, atopic dermatitis, seborrheic dermatitis, stasis dermatitis, drug dermatitis and lymphoma dermatitis. However, it may occur as an idiopathic disease.

Histopathology. The various types of dermatitis rarely present a histologic picture sufficiently diagnostic to allow their differentiation

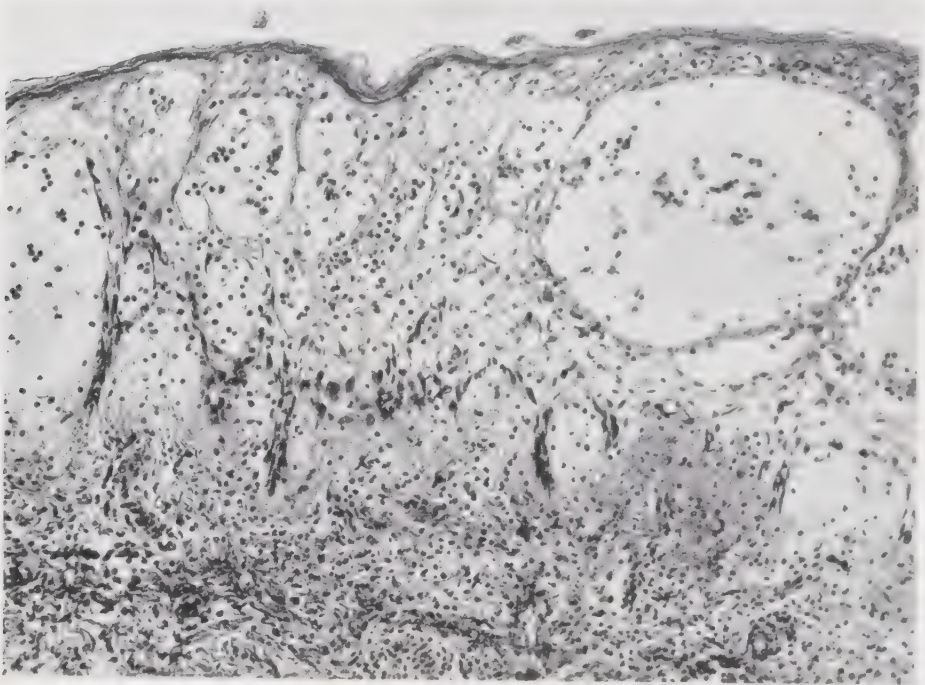


FIG. 24. Acute dermatitis: contact dermatitis due to poison ivy. Numerous intra-epidermally located vesicles and marked intracellular edema are present. The vesicles are separated by thin septa formed by the resisting walls of edematous epidermal cells (reticular degeneration) and thus form a multilocular bulla. ($\times 100$)

because the same histologic reactions occur in all forms of dermatitis: exudation leading to vesiculation in the acute stage; proliferation leading to acanthosis in the chronic stage; and a combination of these two reactions in the subacute stage. Since, as a rule, no more specific diagnosis than acute, subacute or chronic dermatitis can be made, the histologic picture as presented by an acute, subacute and chronic dermatitis will be described first. Thereafter, the distinctive features occasionally presented by the various members of the dermatitis-eczema group will be discussed.

IN ACUTE DERMATITIS, intra-epidermally located vesicles or bullae predominate the histologic picture. Considerable intercellular edema (spongiosis) and intracellular edema (altération cavitaire) may be present in the epidermis surrounding the vesicles. If the number of

vesicles is great and the intracellular edema pronounced, the vesicles, due to reticular degeneration of the epidermis, will be separated from one another only by thin septa formed by the resisting walls of edematous epidermal cells and will thus form a multilocular bulla (Fig. 24). The vesicles and the bullae contain a few lymphocytes, eosinophils and neutrophils and disintegrated epidermal cells. Migrating lymphocytes and neutrophils are present in the epidermis. The cells of the stratum corneum may be parakeratotic and intermingled with fibrin and numerous neutrophils (Winer and Lipschultz). The upper dermis shows vascular dilatation, edema and a predominantly perivascular infiltrate of lymphocytes, eosinophils and neutrophils.

The mode of formation of the vesicles and the bullae in dermatitis-eczema is of interest. Whereas, in the past, it generally had been assumed that spongiosis, i.e., intercellular edema, caused the vesicles, many authors now believe that intracellular liquefaction necrosis is the primary factor and that spongiosis occurs secondarily. In 1925, Civatte described as the primary lesion the "vésiculette primordiale" formed by the lysis of two or three squamous cells through cytoplasmic alteration. Spongiosis followed this and caused enlargement of the cavity. Percival, Drennan and Dodds have expressed the same view and cite the following observations in its support: vesicles tend to form in areas where the rete cells appear liquefied; vesicles often lie in areas formerly occupied by epidermal cells (Fig. 25); and spongiosis may be entirely absent in the vicinity of vesicles. Polak and Mom, studying the formation of vesicles in experimental eczema with the aid of silver impregnation, found that, at the time the vésiculette primordiale formed, the intercellular bridges were still intact and only broke later by mechanical force when the vesicle had increased in size.

Differentiation of acute vesicular or bullous dermatitis from bullous erythema multiforme and dermatitis herpetiformis is not always possible. Although in the latter two diseases the bullae form subepidermally, they may be located intra-epidermally during the stage of healing due to regeneration of the epidermis. In that case, secondary findings, such as the presence of marked spongiosis in contact dermatitis and its absence in the other two diseases and the number of eosinophils may aid in the decision. It should be stressed as of utmost importance that for the diagnosis of all vesicular and bullous diseases an early lesion must be chosen for histologic examination because secondary factors, such as regeneration and pyogenic infection, may obscure the diagnostic features.

IN SUBACUTE DERMATITIS, one sees spongiosis, intracellular edema and, usually also, vesicle formation. However, the vesicles are smaller than in acute dermatitis (Fig. 25). Moderate acanthosis and varying degrees of parakeratosis are present. The inflammatory infiltrate in the dermis usually is pronounced and is composed of a multiplicity of cells: lymphocytes predominate, but neutrophils, eosinophils and

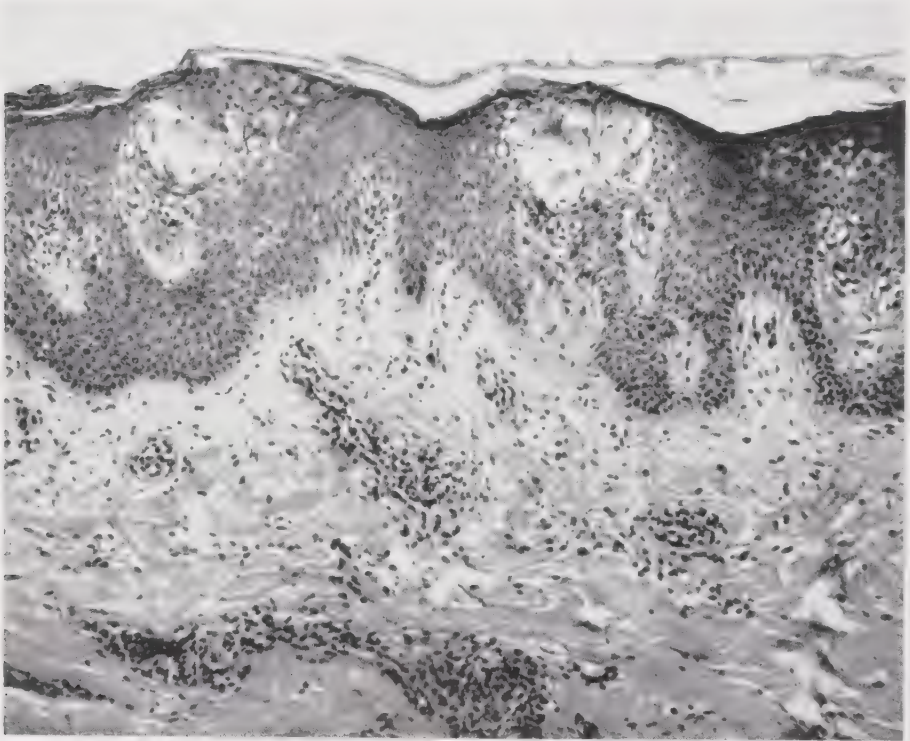


FIG. 25. Subacute dermatitis: nummular eczema. There is intra-epidermal vesicle formation. The vesicles lie in areas formerly occupied by epidermal cells. The epidermis shows parakeratosis and moderate acanthosis. The dermis shows a perivascular infiltrate. ($\times 100$)

histiocytes are also seen. There may be considerable migration of neutrophils and lymphocytes through the epidermis.

IN CHRONIC DERMATITIS, there is often marked acanthosis with elongation of the rete ridges. There is hyperkeratosis intermingled with areas of parakeratosis. Slight intercellular edema may be present in the epidermis, but vesicle formation is absent. In the upper dermis, one sees a moderate amount of predominantly perivascular infiltration composed of various types of cells. Lymphocytes prevail, but the number of eosinophils, histiocytes and fibroblasts may be considerable. Neutrophils are absent. The number of capillaries is increased and the walls of the arterioles and the small arteries may be thickened. The term neurodermatitic reaction has been given by

Sachs, Miller and Gray (1946) to the histologic picture as described above for chronic dermatitis because it is characteristically present in neurodermatitis disseminata (atopic dermatitis) and neurodermatitis circumscripta (lichen simplex chronicus). However, the same histologic picture may occur in any dermatosis belonging to the dermatitis-eczema group.



FIG. 26. Chronic dermatitis: neurodermatitis circumscripta. There are hyperkeratosis, acanthosis, elongation of the rete ridges and elongation and broadening of the papillae. The dermis shows a chronic inflammatory infiltrate and fibrosis. ($\times 50$)

Many diseases not members of the dermatitis-eczema group show, either regularly or occasionally, a histologic picture allowing no more specific diagnosis than chronic dermatitis. Diseases which regularly show the nonspecific histologic picture of chronic dermatitis include pityriasis rosea, parapsoriasis and pellagra. Many other diseases, such as psoriasis, lichen planus and lupus erythematosus, to name but a few, show a diagnostic histologic picture in clinically typical cases but may show a nonspecific histologic picture, that of chronic dermatitis, in clinically atypical cases.

Early mycosis fungoides must always be kept in mind as a possible diagnosis when a section showing chronic dermatitis is examined. It often is a very difficult task to establish or rule out early mycosis

fungoides. One should search for atypical histiocytes (so-called mycosis cells), mitotic figures, clumping of nuclei, karyorrhexis (disintegration of nuclei into "nuclear dust") and Pautrier micro-abscesses. (For further details, see page 485.) However, it should be realized that some atypicality of the histiocytes and an occasional mitotic figure sometimes may be seen in chronic dermatitis. If in doubt, it is always best to request another specimen for histologic examination.

A few words about the histologic aspects of the various members of the dermatitis-eczema group are now in order.

CONTACT DERMATITIS. Contact dermatitis may be acute, subacute or chronic. The histologic descriptions given above for acute, subacute and chronic dermatitis apply in general to contact dermatitis. Acute contact dermatitis presents numerous, closely set, large and small intra-epidermal vesicles (Fig. 24). Chronic contact dermatitis shows irregular acanthosis. Even at that stage, spongiosis and small intra-epidermal vesicles are often present (Sachs, Miller and Gray, 1944; Miller).

NUMMULAR ECZEMA (infectious eczematoid dermatitis). This eruption, characterized clinically by "pinpoint vesicles," usually shows histologically a picture of subacute dermatitis (Fig. 25). In a moderately acanthotic epidermis, one finds numerous scattered areas of intra-epidermal vesiculation (Sachs, Miller and Gray, 1946). As a rule, spongiosis about the vesicles is slight or absent.

ATOPIC DERMATITIS (neurodermatitis disseminata). The histologic picture is usually that of a chronic dermatitis showing acanthosis with varying degrees of spongiosis. The number of eosinophils in the inflammatory infiltrate is often considerable (Burkhart and Montgomery).

LICHEN SIMPLEX CHRONICUS (neurodermatitis circumscripta). The microscopic appearance is essentially that of a chronic dermatitis (Fig. 26). There are hyperkeratosis interspersed with small areas of parakeratosis, acanthosis characterized by rather regular elongation of the rete ridges, and elongation and broadening of the papillae. There may be some spongiosis, but vesiculation does not occur. In addition to a chronic inflammatory infiltrate, the dermis often shows a fair number of fibroblasts and some fibrosis, even in the papillae.

In the hypertrophic type of lichen simplex chronicus (lichenificatio gigantea or lichen corneus hypertrophicus), the epidermis shows, in addition to acanthosis with elongation of the rete ridges, considerable hyperkeratosis and papillomatosis (Shaffer and Beerman; Hyman and Erger).

The histologic picture of lichen simplex chronicus may resemble

that of psoriasis, which shares with lichen simplex chronicus the tendency to elongation of the rete ridges. However, psoriasis shows predominantly parakeratosis rather than hyperkeratosis, thinning of the suprapapillary portions of the stratum malpighii, edema of the upper portions of the papillae and not infrequently Munro micro-abscesses. Furthermore, the papillary capillaries in psoriasis are dilated and tortuous, whereas, in lichen simplex chronicus, they appear normal. According to Stoughton and Wells, the Hotchkiss-McManus stain demonstrates the capillary changes in psoriasis very clearly and thus aids in its differentiation from lichen simplex chronicus.

EXUDATIVE DISCOID AND LICHENOID CHRONIC DERMATOSIS (Sulzberger-Garbe). The epidermis may show spongiosis and vesiculation as in subacute dermatitis, or acanthosis with little or no edema as in chronic dermatitis. The vessels of the upper dermis and the mid-dermis are dilated and their walls thickened. About them is a mantle of lymphocytes, histiocytes, polymorphonuclear neutrophils, eosinophils and numerous plasma cells. Sachs and Kirsch state that the presence of many plasma cells gives the histologic picture a distinctive appearance so that the diagnosis can be established on microscopic findings alone.

SEBORRHEIC DERMATITIS. The histologic picture is not diagnostic. It may be said to be halfway between psoriasis and chronic dermatitis. The horny layer, because of the tendency to desquamation, is only poorly developed and most of its cells are parakeratotic. The epidermis shows slight to moderate acanthosis with elongation of the rete ridges, and slight intracellular edema and spongiosis. The dermis shows a mild chronic inflammatory infiltrate. Munro micro-abscesses and neutrophils migrating through the epidermis, as seen in psoriasis, occasionally are observed. In cases in which the histologic picture resembles that of psoriasis, the presence of spongiosis serves to distinguish seborrheic dermatitis from psoriasis.

STASIS DERMATITIS. Histologic examination shows either a subacute or a chronic dermatitis. Quite frequently, considerable amounts of hemosiderin are present in the dermis. Older lesions may show numerous newly formed capillaries embedded in a fibrotic dermis. Whereas it has been assumed generally that venous and capillary stasis is responsible for the clinical manifestations of stasis dermatitis, Kulwin and Hines, in a study of the vessels at the dermo-subcutaneous junction, found changes more often and more severely in the arterioles than in the venules. The changes in both arterioles and venules consisted of intimal proliferation, endothelial hyperplasia and medial hypertrophy. Complete obliteration of arterioles

was seen in specimens from ulcerated areas. These authors concluded that arteriolar changes may be an important etiologic factor in stasis dermatitis.

GENERALIZED EXFOLIATIVE DERMATITIS. The histologic appearance may be that of a subacute or a chronic dermatitis. In the subacute type, there are parakeratosis, marked intercellular and intracellular edema

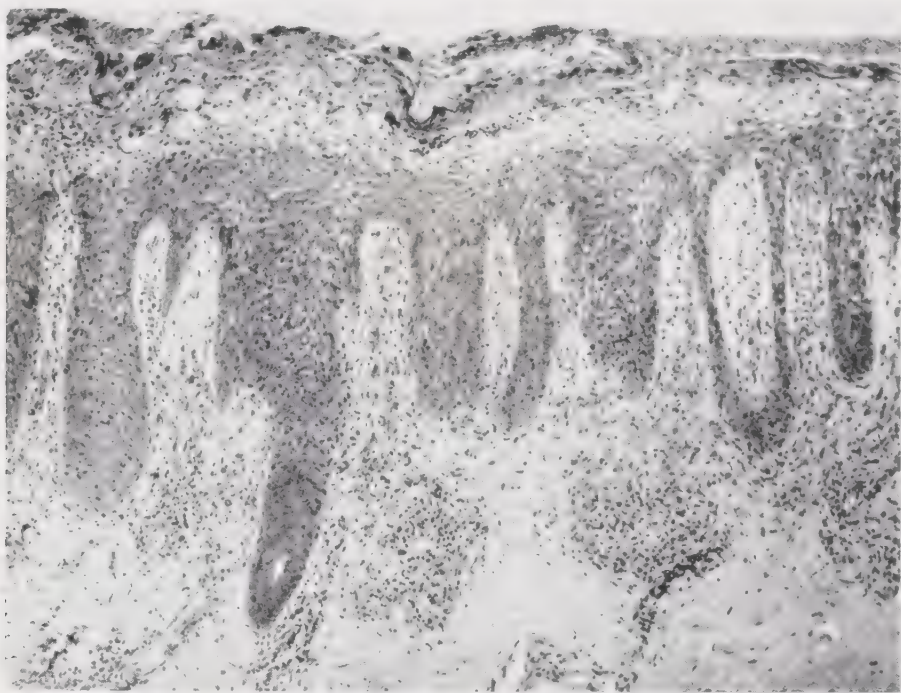


FIG. 27. Generalized exfoliative dermatitis, due to arsphenamine. There are parakeratosis, marked intercellular and intracellular edema in the upper stratum malpighii, acanthosis with elongation of the rete ridges and migration of inflammatory cells through the epidermis. The upper dermis shows edema and a considerable amount of inflammatory infiltrate. ($\times 100$)

edema, particularly in the upper stratum malpighii, acanthosis with elongation of the rete ridges and migration of cells through the epidermis. The upper dermis shows edema and a considerable amount of inflammatory infiltrate (Fig. 27). If the edema in the upper stratum malpighii is pronounced, the cells of the upper stratum may exfoliate together with the parakeratotic horny cells. In the chronic type of exfoliative dermatitis, the histologic picture is that of chronic dermatitis. Each such case requires thorough histologic investigation in order to rule out lymphoma. Montgomery has stated that 25 per cent of all cases of exfoliative dermatitis are proved on histologic examination to be associated with lymphoma. Even if the histologic examina-

tion at first shows no evidence of lymphomatous infiltration in the dermis, it is advisable to perform further biopsies at intervals. (See also page 490.)

DERMATOPATHIC LYMPHADENITIS

Any extensive dermatitis, but particularly generalized exfoliative dermatitis, whether due to lymphoma or not, may cause a generalized lymphadenitis of the subcutaneous lymph nodes.

Histopathology. This lymphadenitis has certain characteristic histologic features not found in other types. It was described first by Pautrier and Woringer as lipo-melanotic reticulosis. Hurwitt introduced the term dermatopathic lymphadenitis.

Histologic examination shows the basic architecture of the lymph node preserved. The cortical lymph follicles possess large germinal centers. The pulp of the lymph node shows considerable hyperplasia of reticulum cells. Since the reticulum cells possess abundant and faintly eosinophilic cytoplasm, the areas of reticular hyperplasia appear as large pale patches (Laipply). The reticulum cells show phagocytic activity and may contain hemosiderin, melanin and, occasionally, fat. The lymph follicles as well as the pulp of the lymph node are permeated with eosinophils, neutrophils and plasma cells. The intermediary sinuses are filled with reticulum cells ("sinus catarrh"). The melanin and the fat occasionally present in the lymph nodes originate in the skin and are carried into the lymphatics by scratching. It has been suggested that the fat may not be sebum but ointment base (Bettley).

Differential Diagnosis. These histologic changes differ from those observed in mycosis fungoides, Hodgkin's disease and follicular lymphoma by the absence of destruction of the basic architecture of the lymph node, the absence of Sternberg-Reed cells and the presence of phagocytic activity in the reticulum cells (Hurwitt). The large lymph follicles present in dermatopathic lymphadenitis differ from those of follicular lymphoma by greater uniformity in size, smaller number and absence of fissures which frequently separate the lymph follicles from the stroma in follicular lymphoma.

In recent years, the relationship of dermatopathic lymphadenitis to lymphoma has been discussed by several authors. Some have assumed that a dermatopathic lymphadenitis can develop into lymphoma (Bluefarb and Webster), and others have regarded cases of generalized erythroderma with dermatopathic lymphadenitis as Brill-Symmers disease (i.e., follicular lymphoma) even in the absence of the histologic criteria of follicular lymphoma (Rost). Neither point of view is justified. Dermatopathic lymphadenitis as such is an en-

tirely nonspecific reaction to an extensive dermatitis. Since lymphoma may manifest itself as an extensive dermatitis (see page 490), it can cause a dermatopathic lymphadenitis. Subsequently, the lymphoma may extend to lymph nodes previously affected by dermatopathic lymphadenitis, but in that case the latter is only chronologically—not etiologically—the forerunner of the lymphoma (Jarrett and Kellett; Keller and Staemmler).

MILIARIA

Miliaria occurs following excessive sweating in parts of the body covered by clothing. There are two types: *miliaria crystallina* and *miliaria rubra*. In *miliaria crystallina*, asymptomatic, small, superficial, noninflammatory vesicles are present. In *miliaria rubra*, the lesions consist of pruritic, discrete but closely aggregated papules, papulovesicles and vesicles surrounded by erythema.

The cause of miliaria lies in excessive hydration of the horny layer by sweat. This results in swelling of the keratin, closure of the narrow sweat pores by keratin and retention of sweat in the sweat ducts.

Histopathology. In *miliaria crystallina*, histologic examination reveals occlusion of the orifices of sweat ducts by keratin plugs and distention of the sweat ducts within the epidermis and, occasionally, also in the dermis. Intracorneal vesicles are present. There is no inflammatory infiltrate. Evidence in favor of the assumption that the intracorneal vesicles contain sweat are the observations in experimental *miliaria crystallina* by Shelley and Horvath that the vesicles on serial sections proved to be in direct communication with sweat ducts and failed to form when sweating was inhibited by the local injection of atropine.

In *miliaria rubra*, an inflammatory infiltrate is present around the sweat ducts in the epidermis and the upper dermis. Either an intra-epidermal or a subepidermal vesicle is seen. It appears that in severe cases of *miliaria rubra*, which are associated with thermogenic anhidrosis, the sweat duct ruptures either within the epidermis leading to an intra-epidermal vesicle or at the epidermal-dermal junction leading to a subepidermal vesicle (O'Brien; Sulzberger, Zimmerman and Emerson). On the other hand, in mild cases the sweat duct does not break, as a rule, but sweat merely escapes from the sweat duct into the epidermis leading to the formation of an intra-epidermal "spongiotic" vesicle (Sulzberger and Zimmerman).

POMPHOLYX (DYSHIDROTIC ERUPTION)

This is a recurrent eruption of numerous deep-seated vesicles occurring singly and in groups on the palms and the soles. Inflam-

matory signs, such as redness and scaling, are absent or slight. Hyperhidrosis is frequently present.

Histopathology. Histologic examination reveals intra-epidermally located vesicles which may lie so close to one another that they are separated only by thin septa of epidermal cells. Around the vesicles the epidermis shows varying degrees of spongiosis.

There has been a long-standing controversy as to whether or not the vesicles of pompholyx are caused by rupture of sweat ducts (and thus are analogous to the vesicles of miliaria) or are simply eczematous ("spongiotic") vesicles. On the basis of recent reports in the literature, the evidence seems to be in favor of the latter view.

The occasional observation of continuity between the lumen of a sweat duct and the cavity of a vesicle has been interpreted by some authors (Whimster) as evidence that the vesicles are of the miliaria type. However, the assumption probably is correct that such continuity represents but a late development. Devine, and also Wilson and Thackray, showed in thorough serial studies that the sweat ducts are singularly spared in the initial stages of vesicle formation and either are displaced to one side of the vesicle or run through the epidermal septa separating two adjoining vesicles. They observed that only after such a septum undergoes necrosis a sweat duct may be seen leading into the vesicle.

PEMPHIGUS

There are two types of pemphigus, each of which has a variant: *pemphigus vulgaris* with pemphigus vegetans and *pemphigus foliaceus* with pemphigus erythematosus. The bullae of pemphigus show acantholysis as a characteristic feature (see Table 2 and Glossary). In contrast, acantholysis is absent in bullous pemphigoid and in benign mucous-membrane pemphigoid, or pemphigus conjunctivae (see pages 85 and 87). However, acantholysis occurs not only in pemphigus but also in Darier's disease, familial benign chronic pemphigus, virus vesicles and, occasionally, senile keratosis.

PEMPHIGUS VULGARIS

Pemphigus vulgaris shows flaccid bullae which break easily and leave denuded areas which tend to increase in size by progressive peripheral detachment of the epidermis. Extensive oral lesions almost invariably are present and often oral lesions are the first manifestation of the disease. Prior to the advent of corticotropin and cortisone, the disease had a very high mortality.

Histopathology. The bullae form intra-epidermally due to a degenerative process affecting the epidermal cells, especially their inter-

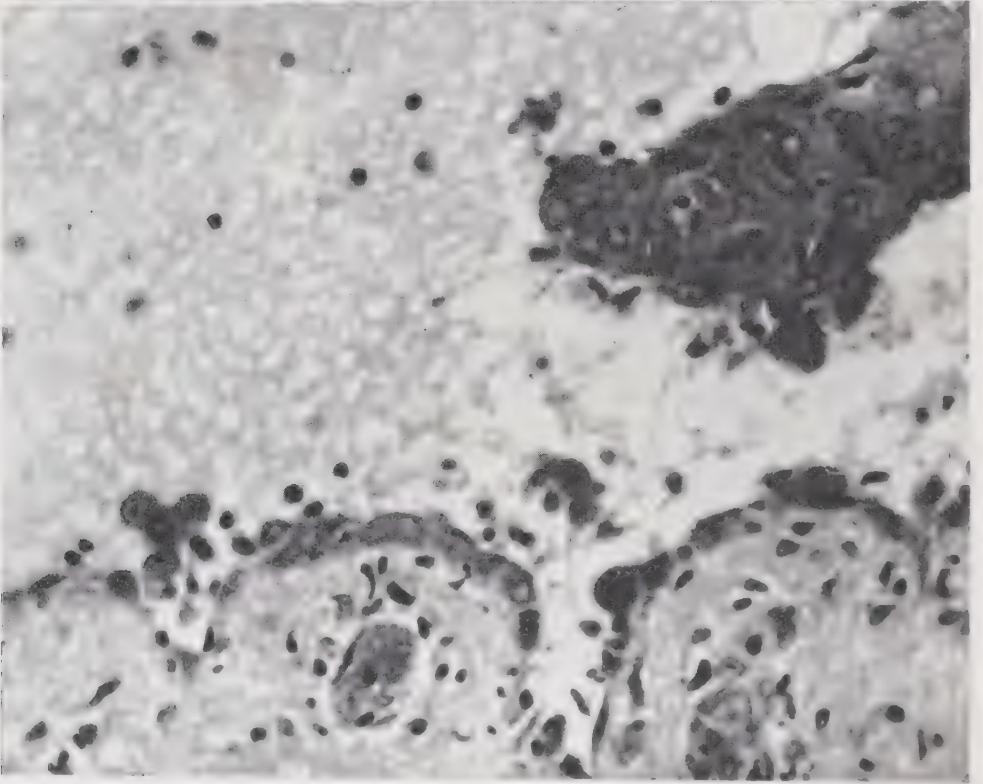
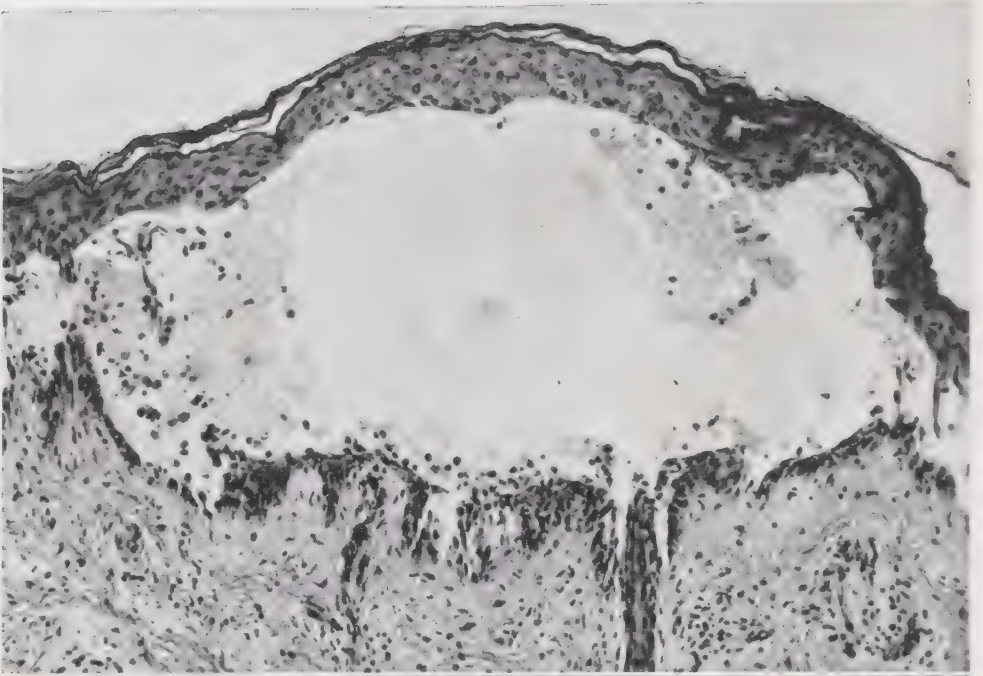
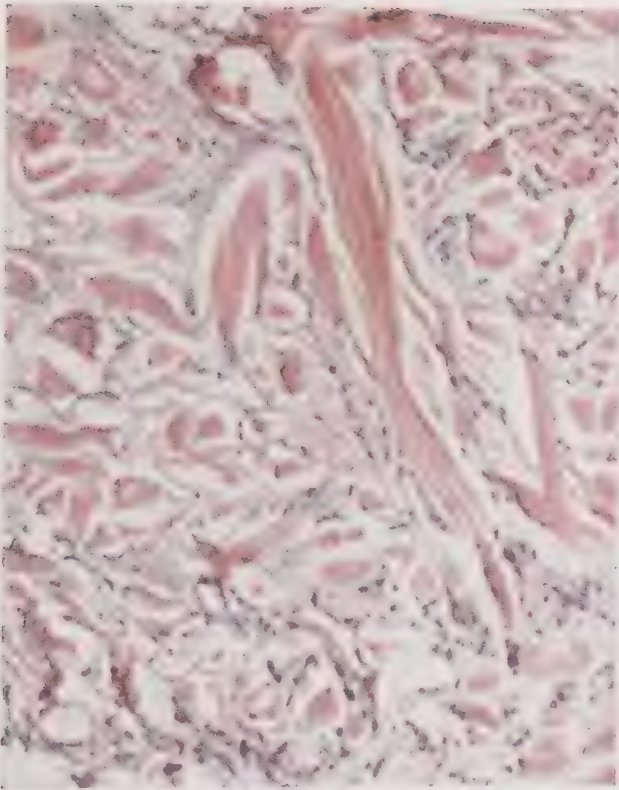
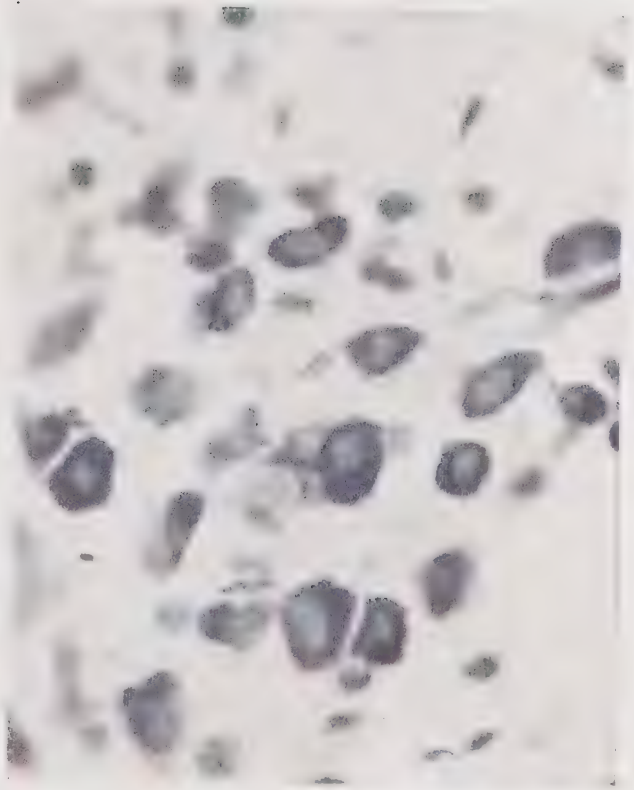


FIG. 28. (*Top*) **Pemphigus vulgaris**. The bulla lies in predominantly supra basal position and leads at its periphery into suprabasal clefts. ($\times 100$)

FIG. 29. (*Bottom*) **Pemphigus vulgaris**. The floor of a bulla shows the basal layer adherent to the dermis. The cavity contains single acantholytic epidermal cells as well as clusters. ($\times 400$)

PLATE I

Urticaria pigmentosa.
Stained with methylene
blue. Numerous baso-
philic granules are pres-
ent in the cytoplasm of
the mast cells. ($\times 800$)



Granuloma annulare.
There is diffuse, incom-
plete degeneration of the
collagen. Fine threads
and granules of mucin
are deposited between
the collagen bundles.
($\times 350$)

cellular bridges (Civatte; Lapière; Cordero; Dupont and Piérard; Lever; Director). The earliest changes consist of intercellular edema and disappearance of the intercellular bridges in the lower stratum malpighii. The resulting loss of coherence between the epidermal cells (acantholysis) results in the formation first of clefts and then of bullae in predominantly suprabasal location (Fig. 28). Due to the

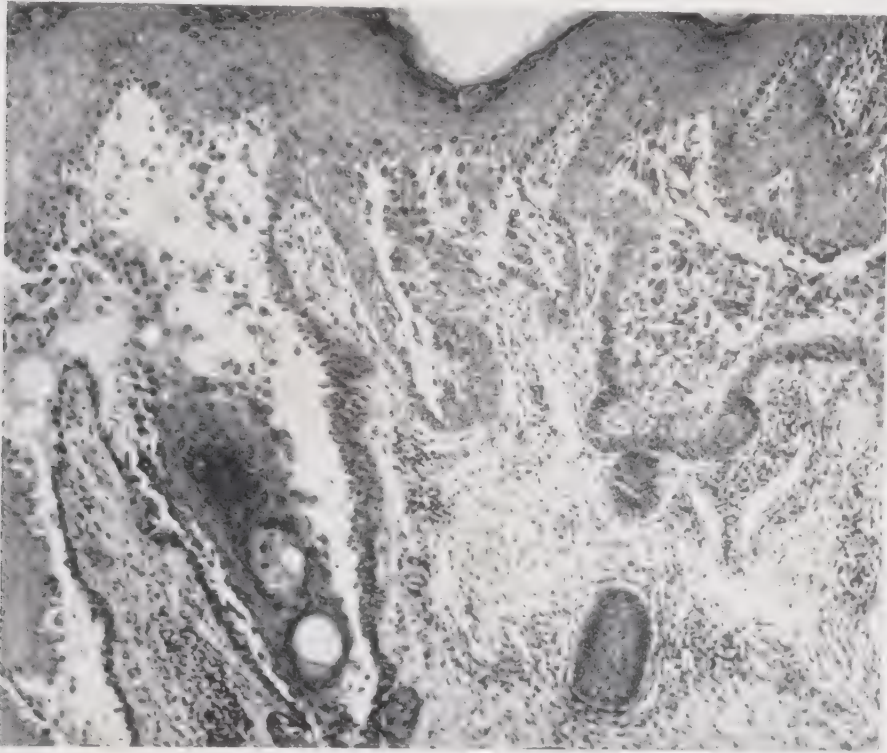


FIG. 30. *Pemphigus vulgaris*. There is an intra-epidermal, predominantly suprabasal bulla. The bulla cavity contains many acantholytic cells. In addition, there is irregular upward growth of papillae lined predominantly by a single layer of epidermal cells, so-called villi. ($\times 200$)

loss of the intercellular bridges, individual cells and clusters of cells drift into the cavity of the bulla. Some of the cells show degenerative changes: their nuclei are round, swollen and hyperchromatic and surrounded by a narrow, sharply demarcated halo of homogeneous cytoplasm (Fig. 29). (These degenerative changes are even more evident when a smear is taken from the base of an early, freshly opened bulla and stained with Giemsa's stain. This, the so-called Tzanck test, often is useful for a rapid, preliminary diagnosis [Blank]. However, it should only supplement, not supplant, histologic examination.) The contour of the floor of the bulla frequently shows, even in early bullae, irregular upward growth of papillae lined by a single layer of

epidermal cells, so-called villi, and downward proliferation of strands of epidermal cells into the spaces between papillae (Fig. 30). Acantholysis may affect also the epithelium of hair follicles, sebaceous glands and sweat glands. As in the surface epidermis, clefts form predominantly right above the basal or outer cell layer.

In older bullae, due to regeneration, the base of the bulla may consist of more than one layer of cells. Denuded areas usually show the basal layer still adherent to the dermis in many places. During the stage of healing, irregular upward proliferation of villi and downward growth of epidermal strands may be present to a considerable degree.

The dermis beneath early bullae usually shows only little inflammation, although a few eosinophils generally are present beneath and within the bullae. In older lesions, the number of inflammatory cells, including eosinophils and plasma cells, may be quite numerous.

Differential Diagnosis. For diagnostic purposes, it is essential that an early bulla be examined—preferably a small bulla which can be excised *in toto*—because secondary changes, induced either by regeneration of epidermal cells or by secondary infection, are absent. The histologic picture of an early bulla of pemphigus vulgaris is highly diagnostic. There are only two conditions which may show the same histologic picture: early pemphigus vegetans and familial benign chronic pemphigus of Hailey and Hailey. Since pemphigus vegetans is but a variant of pemphigus vulgaris, it is quite natural that they resemble each other. However, the histologic resemblance between pemphigus vulgaris and familial benign chronic pemphigus is curious, since there is very little clinical resemblance between the two conditions. For their differentiation, see page 52.

PEMPHIGUS VEGETANS

As a rule, pemphigus vegetans begins and ends as pemphigus vulgaris. It differs from the latter only in that many of the denuded areas heal with the formation of verrucous vegetations which in their early stage are studded with pustules. A relatively benign variant of pemphigus vegetans is pyodermite végétante of Hallopeau: instead of bullae, pustules are the primary lesion. They are followed by the formation of gradually extending verrucous vegetations.

Histopathology. The bullae show the same histologic picture as those of pemphigus vulgaris. Usually, however, they show, to a greater extent than pemphigus vulgaris, formation of villi and downward growth of epithelial strands. The verrucous vegetations are characterized by considerable papillomatosis, acanthosis and irregular downward proliferation of thick strands of epidermis. Acanthol-

sis and formation of clefts are observed only rarely by the time the verrucous vegetations have formed. A striking feature, however, is the presence of intra-epidermal abscesses composed almost entirely of eosinophils (Fig. 31). These abscesses, highly diagnostic of pemphigus vegetans, correspond to the bullae of earlier lesions. The fact



FIG. 31. *Pemphigus vegetans*. The section, obtained from a verrucous vegetation, shows considerable acanthosis and intra-epidermal abscesses composed almost entirely of eosinophils. ($\times 100$)

that usually they are not in a suprabasal position is due probably to the rapid proliferation of the epidermis around and below the abscess cavity (Director). Old vegetations merely show considerable papillomatosis and hyperkeratosis with few or no eosinophils so that the histologic picture is no longer diagnostic.

In the benign variant of pemphigus vegetans, *pyodermite végétante* of Hallopeau, the early lesions, which are pustules arising on normal skin, show considerable acantholysis with formation of small cavities, many in suprabasal position. These cavities are filled with numerous eosinophils and neutrophils as well as degenerated epidermal cells. A pronounced inflammatory infiltrate composed largely

of eosinophils is present in the altered portions of the epidermis as well as in the upper dermis. The verrucous vegetations show the same histologic picture as those of pemphigus vegetans, including the intra-epidermal eosinophil abscesses.

PEMPHIGUS FOLIACEUS

Pemphigus foliaceus begins with flaccid bullae, usually on an erythematous base. Erythema, oozing and scaling are present from

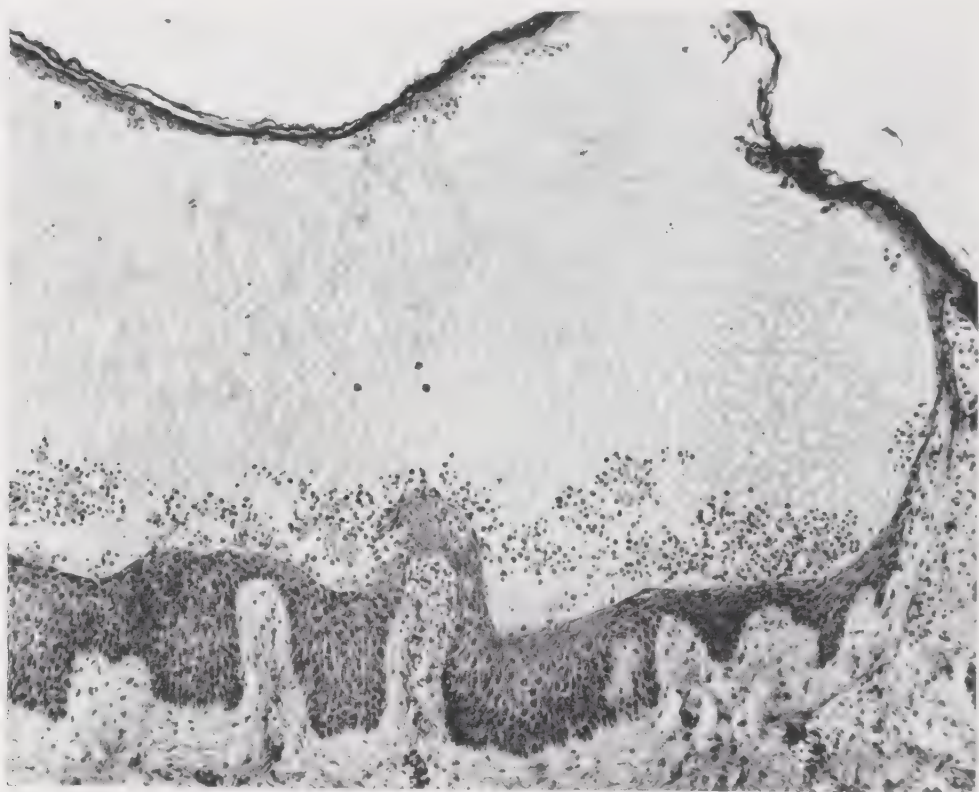


FIG. 32. *Pemphigus foliaceus*. An intact bulla in superficial, partly sub-corneal, position. Acantholysis is present at the base, as well as at the top, of the bulla. ($\times 100$)

the beginning, not only around the bullae but also in other areas. Gradual extension of the lesions leads to involvement of most, if not all, of the body surface. In the advanced stage, bullae are few and may even be absent. Hyperkeratotic areas then often form. Oral lesions occur only very rarely.

Histopathology. The earliest change consists of an area of acantholysis in the upper epidermis, usually in the granular layer or right beneath it, leading to the formation of a cleft in superficial, often subcorneal location (Rook and Whimster; Lever).

This cleft may develop into a bulla in superficial, often subcorneal position with acantholysis present at the floor as well as at the roof of the bulla (Fig. 32). Usually, however, enlargement of the cleft leads to detachment of the uppermost epidermis without bulla formation (Fig. 33). The cells bordering the cleft show absence of intercellular bridges as well as other signs of degeneration and a tendency

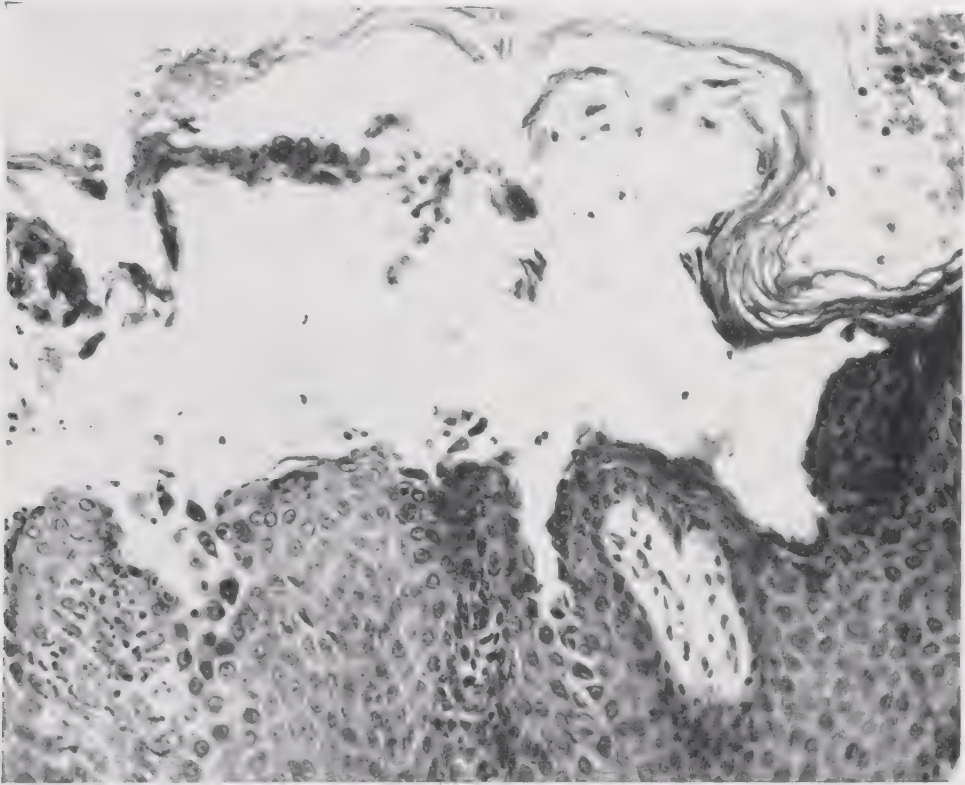


FIG. 33. *Pemphigus foliaceus*. An early lesion showing detachment of the horny and the granular layers without bulla formation. The epidermal cells at the base of the cleft show loss of intercellular bridges resulting in acantholysis. ($\times 200$)

to breaking off into the space formed by the cleft (acantholysis). Occasionally, secondary clefts develop and result in detachment within the middle section of the epidermis. However, detachment immediately above the basal layer or of the entire epidermis does not occur.

Older lesions show acanthosis, a mild degree of papillomatosis and, in addition, hyperkeratosis and parakeratosis. The hyperkeratosis may be considerable and often is associated with keratotic plugging of the follicles. In areas of hyperkeratosis, the granular layer is increased in thickness and frequently shows degenerative changes consisting of acantholysis and of shrinking and hyperchromasia of individ-

ual granular cells. Such granular cells resemble the grains of Darier's disease and are highly diagnostic of pemphigus foliaceus (Fig. 34).

The dermis shows a moderate number of inflammatory cells among which eosinophils are often prominent.

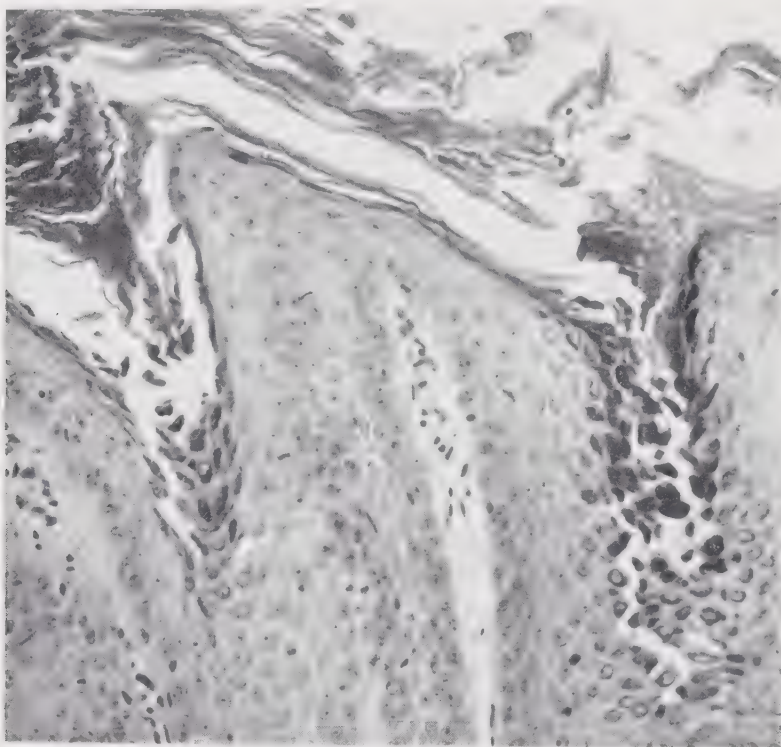


FIG. 34. **Pemphigus foliaceus.** This represents a late lesion showing considerable acanthosis and hyperkeratosis with cleft formation and acantholysis in the granular layer. The granular cells appear shrunken and hyperchromatic and thus resemble the grains of Darier's disease. ($\times 200$)

PEMPHIGUS ERYTHEMATOSUS

Pemphigus erythematosus (Senear-Usher syndrome) represents an abortive form of pemphigus foliaceus which may remain localized or may advance into pemphigus foliaceus. The first lesions usually occur in the center of the face.

Histopathology. The histologic picture is identical with that of pemphigus foliaceus. In older lesions, follicular hyperkeratosis with acantholysis and dyskeratosis of the granular cells is often pronounced (Percival; Lever).

Differential Diagnosis. Although, clinically, the lesions of pemphigus erythematosus may resemble those of lupus erythematosus, they differ sufficiently in their histologic appearance to make a differentiation possible. Both diseases have in common follicular hy-

perkeratosis, but acantholysis and dyskeratosis of the granular cells within the hyperkeratotic plugs are found only in pemphigus erythematosus. On the other hand, hydropic degeneration of the basal cells and a patchy inflammatory infiltrate in the dermis occur only in lupus erythematosus. If bullae are present, they are located high up in the epidermis in pemphigus erythematosus; whereas, in lupus erythematosus, they are subepidermal since they form secondary to the hydropic degeneration of the basal layer.

BULLOUS PEMPHIGOID

This disease is characterized by a more or less generalized eruption of large, tense bullae. When they break, the resulting denuded areas

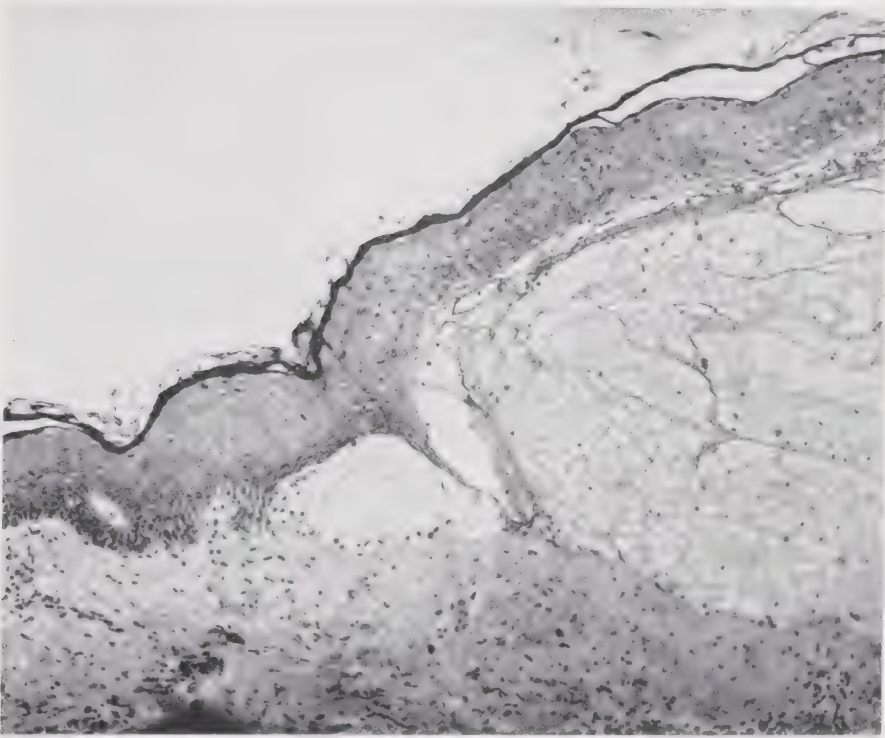


FIG. 35. Bullous pemphigoid. A large subepidermal bulla is shown. On the left one can observe that the accumulated blister fluid pushes the intact epidermis off its dermal moorings. The bulla contains a net of fibrin but only few inflammatory cells. The upper dermis shows edema with very little inflammatory infiltrate. ($\times 100$)

do not increase in size materially, as they do in pemphigus vulgaris; rather, they show a good tendency to heal. Involvement of the oral cavity is usually mild and may be absent. While in aged, debilitated people the disease may result in death, in well-preserved individuals it is chronic, relatively benign and self-limited. Some authors,

especially the French School (Lapière), regard bullous pemphigoid as a bullous variant of dermatitis herpetiformis, although it differs from dermatitis herpetiformis by the lack of polymorphism, by the absence of grouping, and in the distribution of the lesions.

Histopathology. The earliest change consists of a subepidermal vacuole which enlarges into a subepidermal bulla (Lever). Early

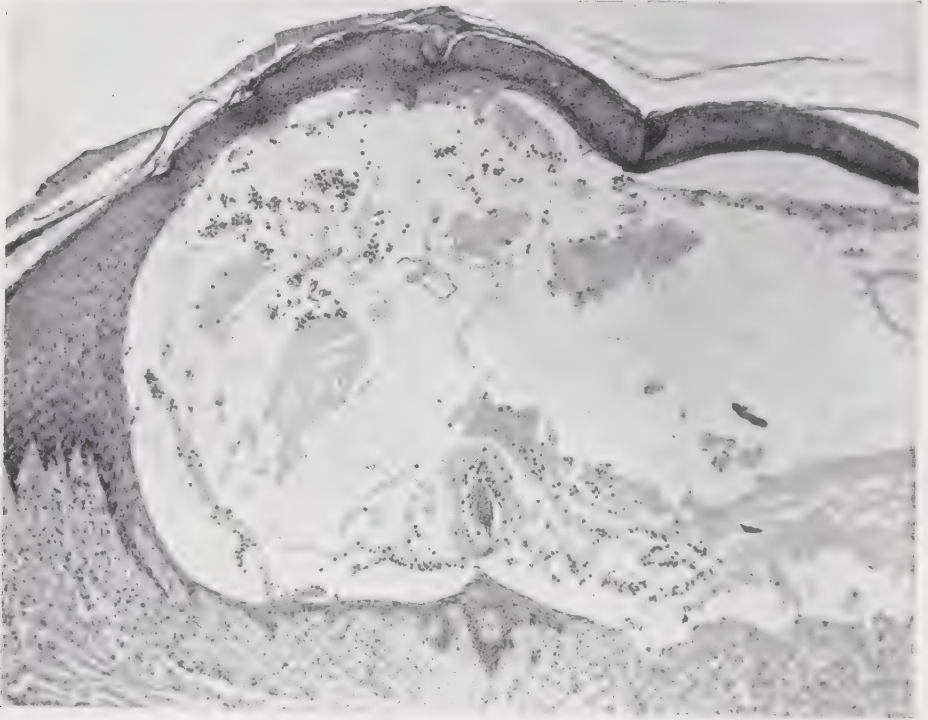


FIG. 36. **Bullous pemphigoid.** The bulla is subepidermal in the center but intra-epidermal at the periphery. In the area where the bulla is intra-epidermal, more than the basal layer is adherent to the dermis, and there is no acantholysis. ($\times 100$)

small bullae, due to pressure of the bulla fluid, often are rounded at their margin and the epidermal cells forming the lateral walls of the bulla appear considerably stretched, without damage, however, to intercellular bridges (Fig. 35). To such rounded bullae, the name pressure bulla has been given. No acantholysis is observed. The epidermis at the roof of the bulla is intact at first, but in older bullae it may become necrotic and disintegrate, with the exception of the horny layer. Also, in older bullae, regeneration of the epidermis takes place at the floor of the bulla, beginning at the periphery and gradually extending over the entire floor (Fig. 36). This regeneration may result in an intra-epidermal location of the bulla; and simultaneous disintegration of the stratum malpighii may cause even a subcorneal location.

The amount of inflammatory infiltrate varies. Most early bullae show only few inflammatory cells in their cavity and in their underlying dermis. Occasionally, however, a rather pronounced infiltrate is present, including many eosinophils.

Differential Diagnosis. As in all vesicular and bullous diseases, it is important that an early lesion be chosen for biopsy; otherwise, due to regeneration of the epidermis, the subepidermal origin of the bulla may no longer be evident. The diagnostic value of a subepidermal, non-acantholytic bulla is limited because this type of bulla occurs in several unrelated diseases, such as benign mucous-membrane pemphigoid, dermatitis herpetiformis, erythema multiforme, epidermolysis bullosa and porphyria cutanea tarda. (See Table 2, page 65.) Even the number of eosinophils in the inflammatory infiltrate within and beneath the bulla is unreliable as a means of differentiation: although eosinophils are present in considerable number in most cases of dermatitis herpetiformis, there may be only a few in some; and in some instances of erythema multiforme and bullous pemphigoid the number of eosinophils may be considerable.

The most important purpose of histologic examination in most cases of bullous pemphigoid is the exclusion of pemphigus vulgaris. As a rule, this is accomplished easily because the structure of these two types of bullae is totally different. In pemphigus vulgaris, the primary change takes place within the epidermis and consists of a degeneration of epidermal cells, particularly of their intercellular bridges, thus leading to acantholysis and bulla formation inside the epidermis. On the other hand, in bullous pemphigoid, the primary change consists of a subepidermal vacuole which enlarges into a bulla. Acantholysis is absent and changes in the epidermis are secondary.

BENIGN MUCOUS-MEMBRANE PEMPHIGOID (PEMPHIGUS CONJUNCTIVAE)

Bullous lesions and denuded areas are present on the mucous membranes. In about half of the cases, lesions are present also on the skin. Scarring commonly develops on the conjunctivae, which frequently but not invariably are involved; and it occurs occasionally on other mucous membranes and on the skin. The disease is very chronic, but, as a rule, the general health is not impaired.

Histopathology. The bullae are subepidermal, with no acantholysis in the epidermis (Lever). Some of the specimens show considerable inflammatory infiltration and, in the later stages, fibrosis of the upper dermis. It is likely that the severity of the inflammation is responsible for the scarring that frequently develops in the lesions of benign mucous-membrane pemphigoid.

DERMATITIS HERPETIFORMIS

Dermatitis herpetiformis is a chronic, recurrent, pruritic disease displaying in symmetrical distribution groups of papules and vesicles on erythematous bases. In rare instances, bullae are present. The extensor surfaces of the extremities, the shoulders and the buttocks are affected predominantly.

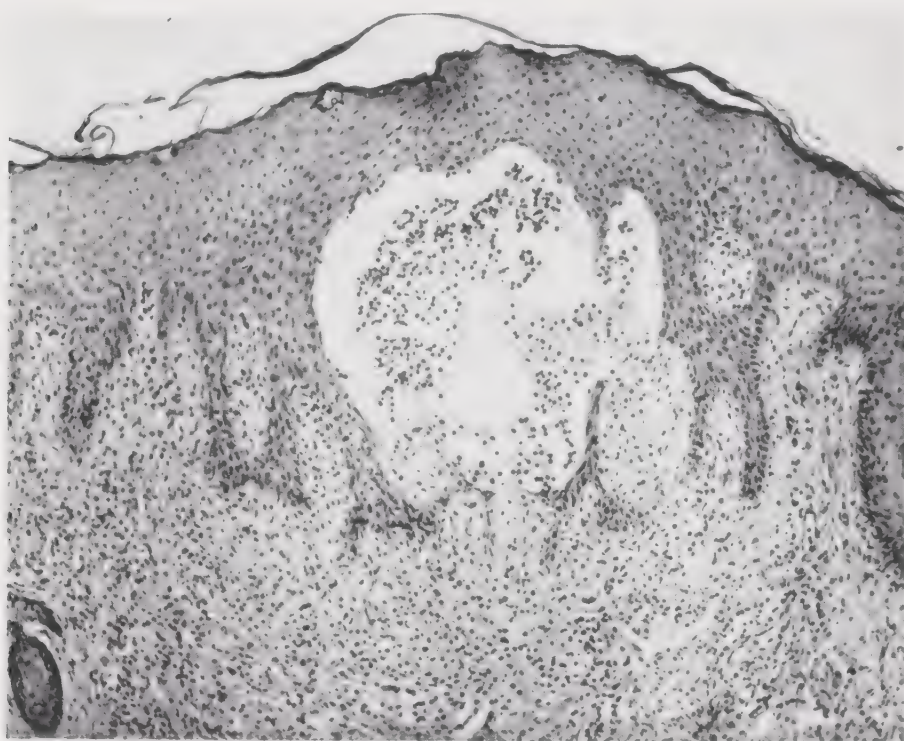


FIG. 37. **Dermatitis herpetiformis.** A subepidermal vesicle is shown. The cells within the vesicle are predominantly eosinophils. The upper dermis shows edema and a considerable cellular infiltrate. ($\times 100$)

Herpes gestationis is the term applied to dermatitis herpetiformis occurring in pregnant women. As a rule, the lesions are vesicular but they may be bullous.

Histopathology. The vesicles and the bullae form without acantholysis beneath the epidermis as subepidermal pressure bullae (see "Classification of Bullae," page 66, and "Bullous Pemphigoid," page 86) (Fig. 37). Older bullae, due to regeneration of the epidermis at their base, may lie intra-epidermally.

The dermis as well as the cavity of the bulla usually show, even in the earliest lesion, a considerable cellular infiltrate in which eosinophils are prominent. However, in some cases the number of eosinophils is small (Burkhart and Montgomery).

Differential Diagnosis. Dermatitis herpetiformis cannot be diagnosed with certainty through histologic examination because subepidermal, non-acantholytic bullae occur in a variety of other diseases (see page 87), and, in two of them (erythema multiforme and bullous pemphigoid), may be associated with a large number of eosinophils. Older lesions, due to the presence of intra-epidermal bullae, may be difficult to differentiate from an acute or a subacute dermatitis. Therefore, it is important that a specimen for biopsy be taken from an early lesion.

ERYTHEMA MULTIFORME

Erythema multiforme is a self-limited, acute dermatosis the lesions of which, as the name implies, are multiform and include macules, papules, vesicles and bullae. The most common lesion is a papule, which, by peripheral extension and central clearing, tends to form the characteristic iris lesion. Occasionally, the lesions are hemorrhagic.

Histopathology. The histologic appearance varies with the clinical aspect. In macular and papular lesions, the epidermis shows spongiosis and intracellular edema, and the dermis edema and an inflammatory infiltrate the severity of which varies according to the clinical manifestations. It is perivascular in arrangement and is composed mainly of lymphocytes but may contain neutrophils and eosinophils.

In hemorrhagic lesions of erythema multiforme one observes, in addition to the above-described findings, extravasation of erythrocytes into the dermis. The histologic picture in these cases may resemble that of anaphylactoid purpura (see page 127) because of the presence of degenerative changes in the endothelial cells of capillaries and perivascular accumulations of neutrophils and eosinophils showing karyorrhexia (vasculitis).

In bullous lesions, the bullae form subepidermally by detachment of the entire epidermis (pressure bulla; see "Classification of Bullae," page 66, and "Bullous Pemphigoid," page 86). However, in older lesions, the bullae may be found within the epidermis due to regeneration of the epidermis at the floor of the bulla. The detached epidermis often shows necrosis of epidermal cells but never acantholysis as in pemphigus vulgaris.

Differential Diagnosis. Differentiation of bullous erythema multiforme from dermatitis herpetiformis and bullous pemphigoid is impossible since in all three conditions the mechanism of bulla formation is the same. However, in the presence of a great number of eosinophils within and beneath the bulla, dermatitis herpetiformis or bullous pemphigoid are more likely to be the diagnosis than erythema multiforme.

BURN

Three degrees are generally recognized. A first-degree burn shows erythema and edema, and a second-degree burn vesicles and bullae. In a third-degree burn, the surface of the skin may be pale gray due to ischemia; purple or brown due to extravasation of blood; or black due to carbonization of the skin.

Histopathology. In a first-degree burn, the earliest change consists of hydropic swelling of the nuclei of epidermal cells with displace-

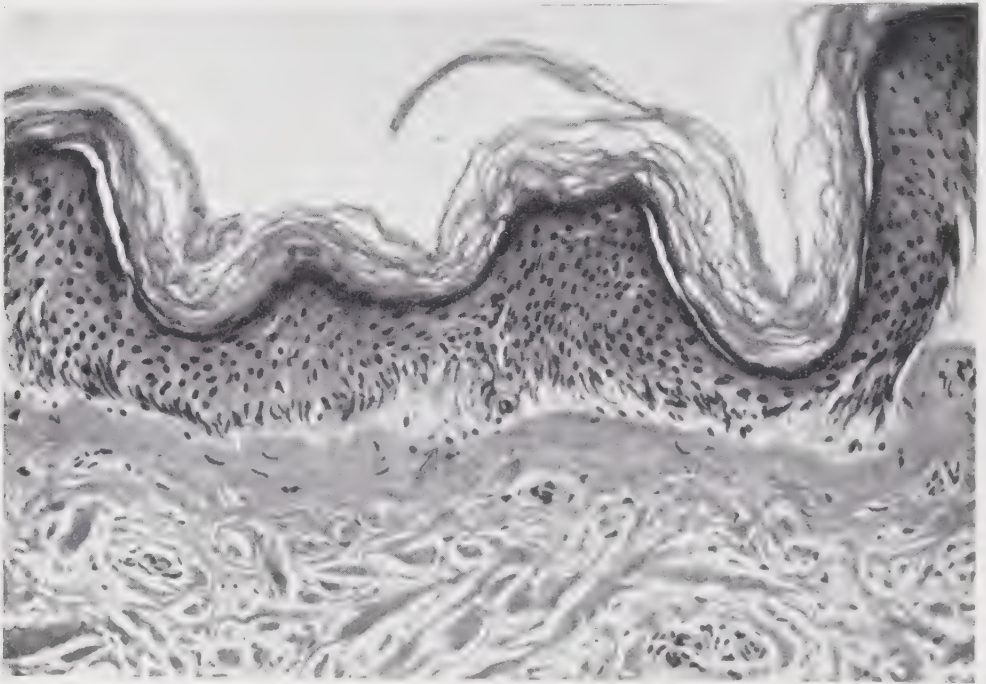


FIG. 38. Burn, second-degree. There is a subepidermal bulla which has an appearance diagnostic of burns because a fringe of uprooted cytoplasmic processes protrudes from the lower ends of the detached basal cells. ($\times 200$)

ment of the chromatin to one side of the nuclear membrane. In severer cases, one observes pyknosis of nuclei throughout the epidermis and disintegration of the cytoplasm of basal cells. The dermis shows hyperemia of the superficial capillaries with occasional extravasation of erythrocytes.

In a second-degree burn, the same changes are present as in a first-degree burn. In addition, there are subepidermal bullae. They have a diagnostic appearance because a fringe of uprooted cytoplasmic processes protrudes from the lower ends of the detached basal cells into the bulla cavity (Fig. 38). The processes appear to have been pulled out of their anchorage in the superficial dermal feltwork of reticulum fibers (Moritz). It may be concluded that damage to the

subepidermal reticulum feltwork is the main reason for the formation of bullae in burns.

In a third-degree burn, coagulation of the epidermis occurs and prevents the nuclear changes and the development of bullae seen in first- and second-degree burns. If the burn is severe, the epidermis may be desiccated and even carbonized. The dermis shows swelling and homogenization of the collagen and either hyperemia of the capillaries with extravasation of red cells or occlusion of the capillaries due to swelling of their walls, resulting in ischemia. At a later stage, leukocytes migrate into the zone of denatured collagen.

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8

Noninfectious Inflammatory Diseases

URTICARIA

Urticaria is characterized by the presence of transient edematous macules or wheals, and is accompanied by considerable itching.

Histopathology. An urticarial wheal shows edema, particularly of the upper dermis. The collagen bundles as well as the individual fibers are separated by edema. The collagenous substance appears swollen and stains poorly. In early wheals, i.e., those only a few minutes old, one finds either no inflammatory reaction or merely a slight perivascular infiltrate composed of lymphocytes. Wheals an

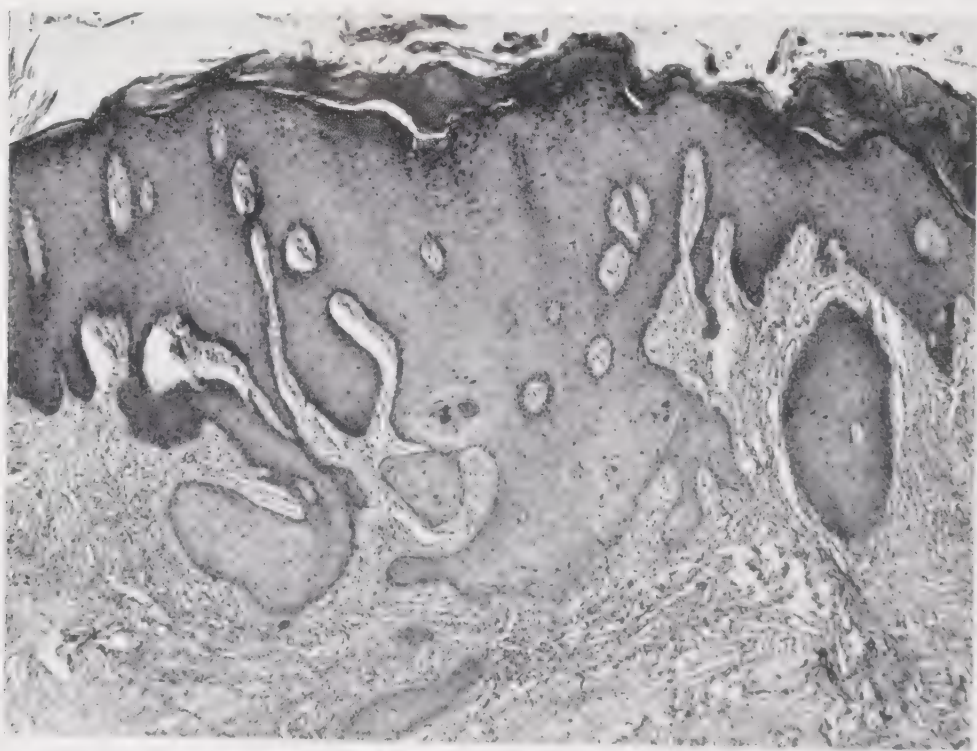


FIG. 39. **Prurigo nodularis.** There are hyperkeratosis and considerable acanthosis with irregular downward proliferation of the epidermis approaching pseudo-epitheliomatous hyperplasia. ($\times 100$)

hour old or older show a mild or even moderately severe lymphocytic infiltrate around the capillaries (Török and Lehner).

PRURIGO NODULARIS

There are discrete, raised, firm, hyperkeratotic lesions, usually from 2 to 10 mm. in size but occasionally larger. They occur chiefly on the extremities and are intensely pruritic.

Histopathology. One observes pronounced hyperkeratosis and acanthosis. There may be deep invaginations of the horny layer, giving the lesion a papillomatous appearance. The epidermis may show irregular downward proliferation (Fig. 39) approaching pseudoepitheliomatous hyperplasia (see page 334). The dermis shows a non-specific inflammatory infiltrate with proliferation of fibroblasts.

It is possible that the disease is a variant of lichen simplex chronicus (see page 72) in which the acanthosis and the hyperkeratosis are greatly accentuated (Shaffer and Beerman).

ERYTHEMA NODOSUM

The lesions consist of tender, red or livid red nodes which are slightly raised above the level of the skin. They vary from 1 to 5 cm. in diameter and usually are limited to the anterior surfaces of the legs; they may, however, occur elsewhere. They involute within a few weeks without breaking down.

Histopathology. The histologic changes are located mainly in the upper portion of the subcutaneous tissue. The dermis merely shows a moderate amount of perivascular infiltrate composed predominantly of lymphocytes.

In early lesions, one observes in the upper portion of the subcutaneous tissue a scattered infiltrate consisting mainly of neutrophils and lymphocytes. Some histiocytes and occasionally eosinophils are present, but plasma cells are absent. The inflammatory infiltrate extends, as the disease progresses, both upward toward the fatty tissue around the sweat glands and downward along and within the fibrous septa of the subcutaneous tissue. The infiltrate, as a rule, is not massive but is divided into numerous small, scattered aggregates of irregular outline. No abscess formation or necrosis occur.

The blood vessels, especially the veins, may show severe involvement, so that many authors believe that a vasculitis represents the primary and predominant lesion (Rotnes; Grzybowski). Other authors, however, state that the blood vessels are not necessarily affected severely and may show only mild involvement (Pautrier and Woringen; Löfgren and Wahlgren). In cases with vascular changes, one observes, especially in the larger veins, invasion of the vascular

walls by the inflammatory infiltrate and marked endothelial proliferation (Fig. 40). However, complete occlusion and thrombosis are rare.

Epithelioid and giant cells are absent in early lesions. However, occasionally one finds small nodules composed of histiocytes lying either in radial arrangement, or in palisade-like arrangement around

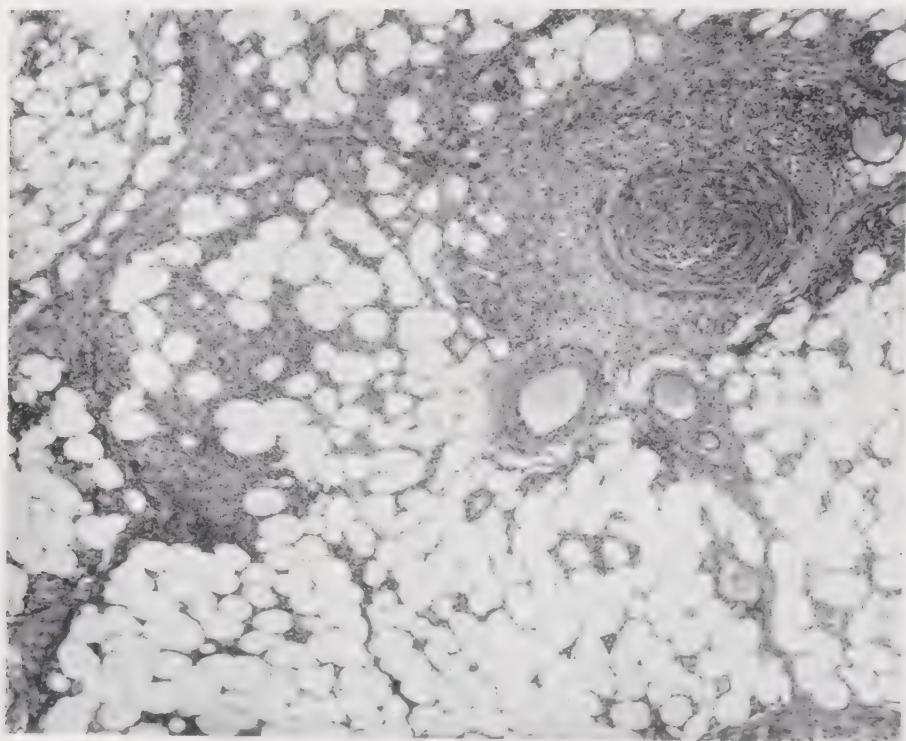


FIG. 40. **Erythema nodosum.** A nonspecific inflammatory infiltrate extends in small, scattered patches through the subcutaneous fat. A large subcutaneous vein shows endothelial proliferation and invasion of its wall by inflammatory cells. ($\times 50$)

a small central fissure (Fig. 41) (Miescher). Not infrequently, these nodules are permeated by neutrophils. Since they are found in no other disease, they are of considerable diagnostic value (Nubé).

Older lesions show fewer neutrophils and more lymphocytes than young lesions. Often, giant cells are present at this stage. The giant cells, usually of the foreign-body type, may be found outside of, or within foci of, epithelioid cells. In the latter case, the arrangement simulates that found in tuberculosis (Rotnes). However, caseation is always absent.

Differential Diagnosis. For differentiation from erythema induratum, see page 186. In cases of erythema nodosum showing severe vascular involvement, periarteritis nodosa must be excluded. In the

latter disease, however, the arteries are predominantly involved, one observes necrosis of vascular walls and the infiltrate usually contains a large percentage of eosinophils. Nodular vasculitis greatly resembles the late stage of erythema nodosum. It differs from erythema nodosum by showing a larger degree of vascular involvement, including in-

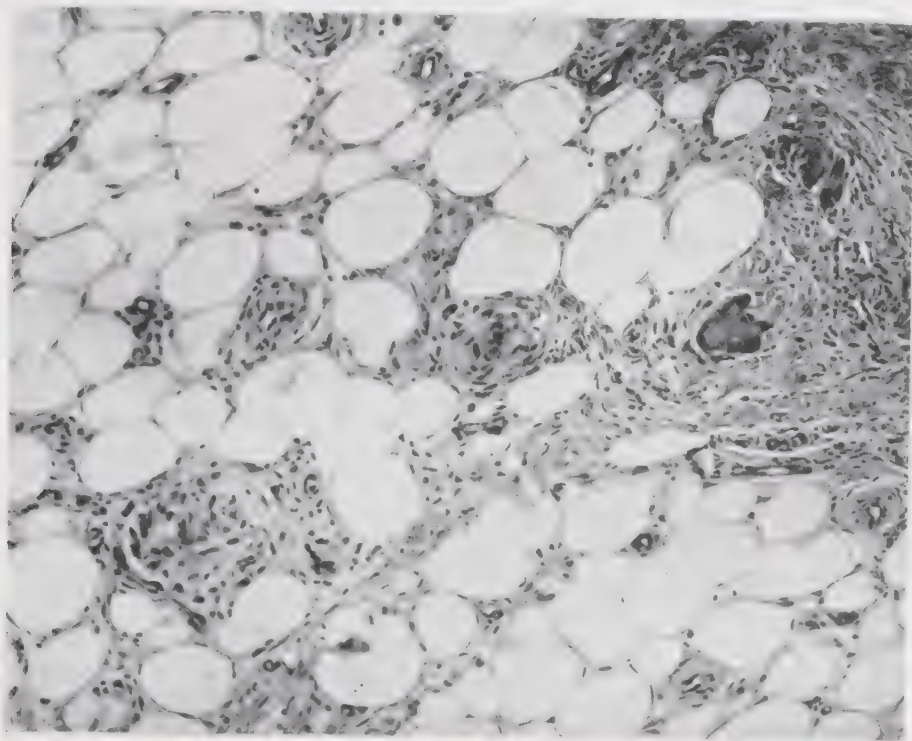


FIG. 41. Erythema nodosum. An older lesion shows two small nodules composed of histiocytes and, to the right, several giant cells of the foreign-body type. ($\times 200$)

volvement of vessels of large caliber. However, it is possible that it represents a variant of erythema nodosum.

NODULAR VASCULITIS

Clinically, this disease is characterized by slightly painful nodules occurring chiefly on the legs. They generally persist for several months. Ulceration does not occur, but recurrence is common.

Histopathology. The lesions show evidence of vasculitis with varying degrees of thickening and obliterative changes in both veins and arteries (Fig. 42). In addition, one observes a varying degree of fibrosis of the subcutaneous tissue and collections of foreign-body giant cells but no tubercle formation. Necrosis of fatty tissue is usually absent but may be present to a mild degree (Woodburne and Philpott; Irgang).

It is probable that nodular vasculitis is a variant of erythema nodosum. For their differential diagnosis see under erythema nodosum, see page 97.

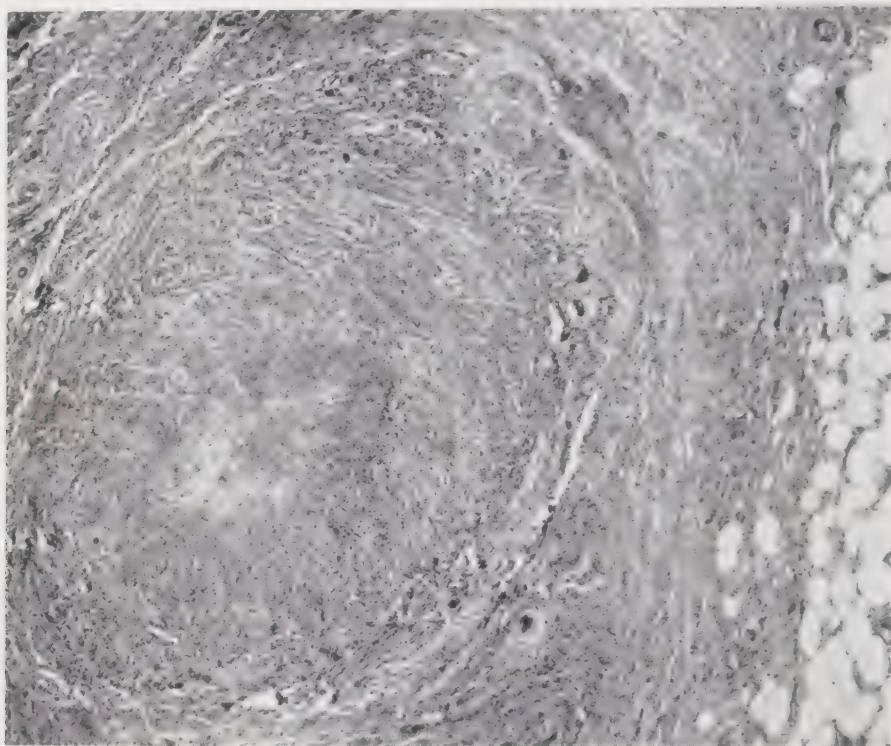


FIG. 42. **Nodular vasculitis.** The wall of a large subcutaneous vein is greatly thickened and infiltrated with inflammatory cells. The lumen is obliterated. ($\times 50$)

PSORIASIS

Psoriasis is a chronic disorder characterized by dull red or brownish papules and plaques. The lesions are sharply demarcated, dry and usually covered with layers of fine silvery scales. As the scales are removed by gentle curettage, one frequently sees characteristic fine bleeding points. In severe cases, the disease may affect the entire skin and present the clinical picture of generalized exfoliative dermatitis (exfoliative psoriasis).

Histopathology. Histologically, psoriasis is characterized by (1) parakeratosis, (2) thinning of the suprapapillary portions of the stratum malpighii, (3) elongation of the rete ridges, (4) edema and clubbing of the papillae and (5) Munro micro-abscesses (Fig. 43).

Corresponding to the layered silvery scaling observed clinically, the horny layer is considerably thickened and consists predominantly of parakeratotic cells, arranged in lamellae with air spaces in between.

The presence of these air spaces is the cause of the silvery appearance of the scales. In old, quiescent lesions, hyperkeratosis may outweigh the parakeratosis. Wherever there is parakeratosis, the granular layer is absent.

The stratum malpighii is thinned above the papillae, often to only two or three layers of cells. The rete ridges show considerable elongation. They often are slender in their upper portion and thickened in

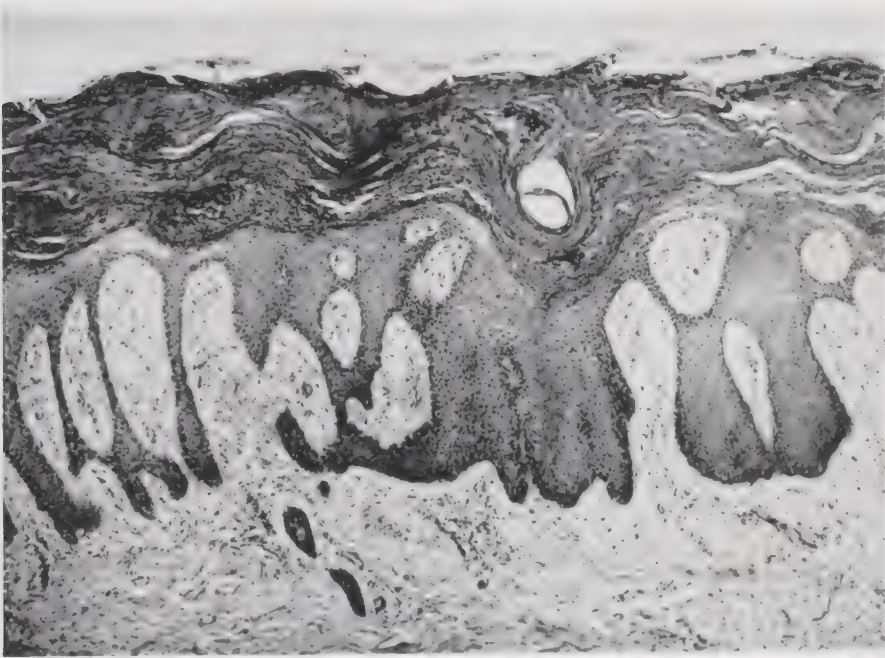


FIG. 43. Psoriasis. Low magnification. There is parakeratosis. The rete ridges are elongated and thickened in their lower portion. There are edema and clubbing of the papillae. ($\times 50$)

their lower portion. They may show branching at their bases, causing neighboring rete ridges to coalesce. There is little or no spongiosis, but intracellular edema often is pronounced in the stratum malpighii overlying the papillae. In early lesions, neutrophils and lymphocytes may be found scattered through the stratum malpighii.

Corresponding to the elongation and the branching of the rete ridges, the papillae are elongated and tortuous. The upper part of the papillae is edematous and club-shaped. The capillaries in the papillae are dilated and tortuous and show slight thickening of their walls. These changes in the capillaries can be demonstrated best by the use of the Hotchkiss-McManus stain (Stoughton and Wells). A mild to moderately severe inflammatory infiltrate is present in the upper dermis, particularly in the papillae. It consists of lymphocytes

and histiocytes, except in early lesions which, in addition, show polymorphonuclear leukocytes in the infiltrate. Plasma cells are found only rarely and eosinophils hardly ever.

The Munro micro-abscesses (Fig. 44) are located either in the stratum corneum or directly beneath it. They represent small ac-

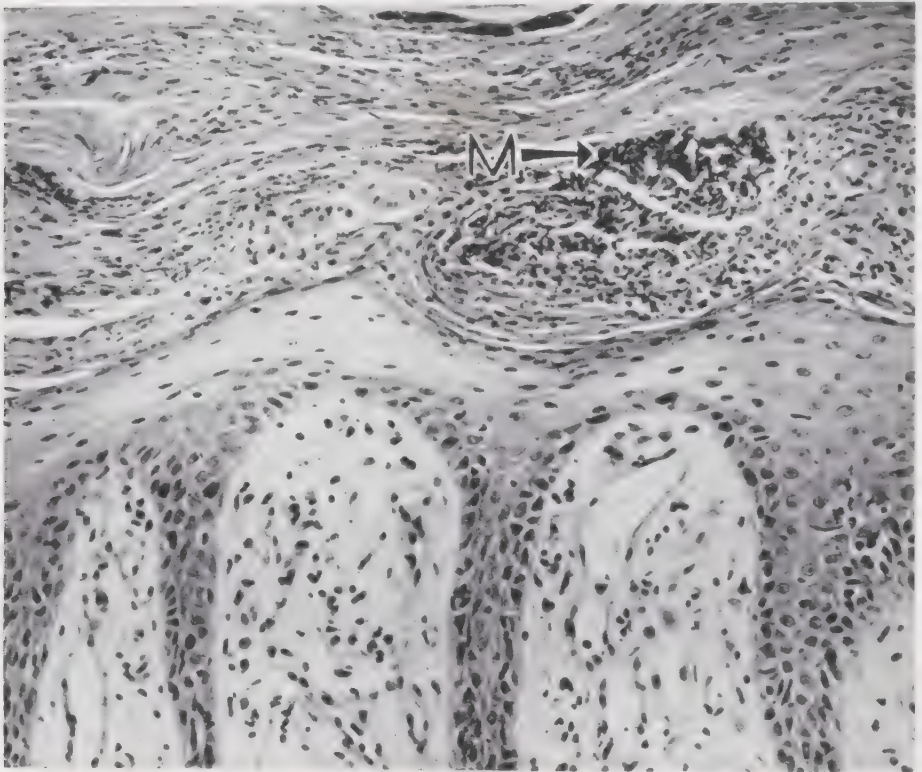


FIG. 44. Psoriasis. High magnification of Figure 43. A Munro micro-abscess (M.) is located within the parakeratotic horny layer. The supra-papillary portions of the stratum malpighii are thinned and show intra-cellular edema. Inter-cellular edema, however, is absent. The capillaries in the tips of the papillae are dilated. ($\times 200$)

cumulations of neutrophils which have migrated there through the epidermis. Munro micro-abscesses, as a rule, are found easily in early lesions. In older lesions, they are few in number or even absent. Thus, their absence does not rule out psoriasis. Neither does their presence establish a diagnosis of psoriasis, since Munro micro-abscesses may occur also in seborrheic dermatitis, acrodermatitis continua (Hallopeau), keratosis blennorrhagica and parapsoriasis guttata.

The bleeding points which may be produced by gentle scraping of the skin correspond to the apices of papillae. They are due to the following histologic changes: (1) parakeratosis, (2) thinning of the stratum malpighii above the tips of the papillae, (3) intracellular

edema of the rete cells overlying the papillae and (4) capillary dilatation in the tips of the papillae.

EXFOLIATIVE PSORIASIS. The histologic picture of exfoliative psoriasis may still show enough of the characteristics of psoriasis to allow this diagnosis. Frequently, however, the appearance is indistinguishable from that of exfoliative dermatitis due to other causes.

Differential Diagnosis. The histologic picture of psoriasis may resemble that of lichen simplex chronicus. For their differentiation, see page 73. Differentiation from seborrheic dermatitis is not always possible. Seborrheic dermatitis may show all the features of psoriasis, though less pronounced than in psoriasis. In addition, however, one finds a fair degree of spongiosis, which in psoriasis is either very slight or absent.

PUSTULOSIS PALMARIS ET PLANTARIS (PUSTULAR PSORIASIS, PUSTULAR BACTERID)

Two diseases have been described in the literature under the name of pustular psoriasis: generalized pustular psoriasis and pustular

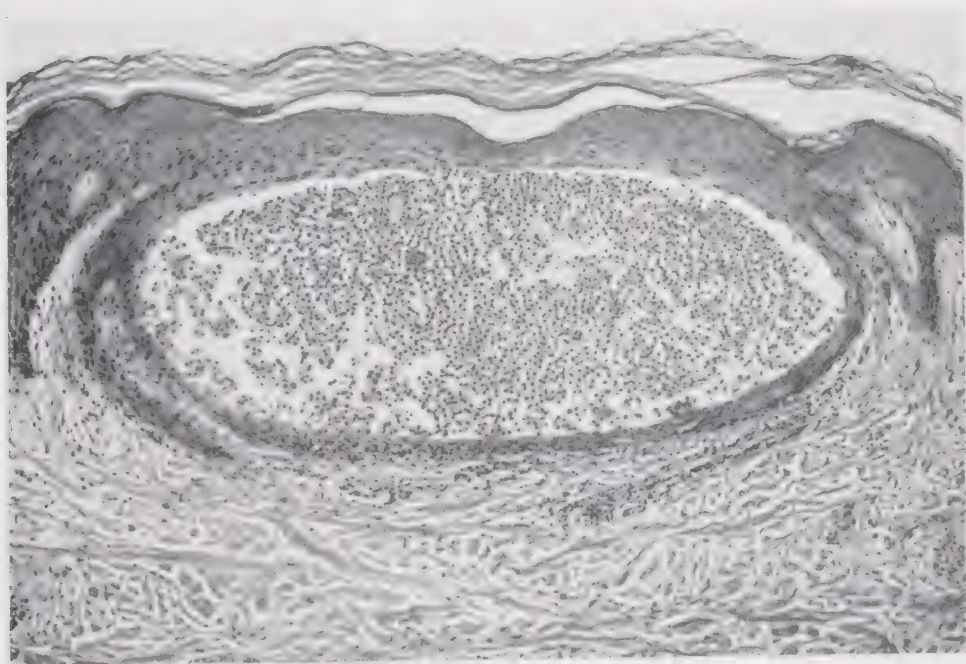


FIG. 45. Pustulosis palmaris et plantaris (pustular bacterid). A large, intra-epidermal, unilocular pustule containing many neutrophils is present. ($\times 100$)

psoriasis of the palms and the soles. Neither of them, however, is a form of psoriasis. Actually, pustular lesions do not occur in psoriasis.

So-called generalized pustular psoriasis is identical with the gen-

eralized form of acrodermatitis continua (Lapière; Brück) and will be described there (see below).

Pustular psoriasis of the palms and the soles, a term introduced by Barber, is a misnomer. This disease is now referred to frequently as either pustular bacterid (Andrews) or acrodermatitis pustulosa (Sachs, MacKee and Rothstein). The term pustulosis palmaris et plantaris is preferable, however.

Pustulosis palmaris et plantaris is a chronic, indolent disorder limited to the palms and the soles and characterized by the appearance of crops of deep-seated pustules within areas of erythema and scaling.

Histopathology. The histologic picture does not resemble that of psoriasis. A large, intra-epidermal, unilocular pustule is present (Fig. 45). It contains many neutrophils and disintegrated cellular elements. The epidermis surrounding the pustule shows slight acanthosis with little or no spongiosis. In the dermis underlying the pustule, a moderately severe inflammatory infiltrate is present, composed mainly of lymphocytes and histiocytes but containing also a few neutrophils. Histologic features of psoriasis, such as parakeratosis, elongation of the rete ridges, thinning of the suprapapillary portions of the stratum malpighii and dilatation of the papillary capillaries are always absent (Sachs and Scannone; Sachs, MacKee and Rothstein).

ACRODERMATITIS CONTINUA

(Hallopeau)

Acrodermatitis continua of Hallopeau, a chronic disease having pustules as a primary lesion, usually is limited to the hands and the feet. The distal portions of the fingers and the toes are predominantly involved. Occasionally, however, the disease is generalized. The affected areas are dark red, dry, shiny and scaling and are studded with shallow pustules. Lesions located on the distal portions of the fingers and the toes may cause atrophy of the skin and loss of nails.

Histopathology. The epidermis shows parakeratosis and moderate acanthosis with elongation of the rete ridges. An inflammatory infiltrate containing many neutrophils but few or no eosinophils is present in the dermis. Many neutrophils are seen invading the epidermis.

However, the characteristic lesion consists of the so-called spongi-form pustule of Kogoj. This type of pustule forms in the uppermost stratum malpighii through the migration of neutrophils into edematous squamous cells. This invasion causes disintegration of the cytoplasm and of the nucleus but not of the cellular walls. The cellular

walls thus form a sponge-like network in the interstices of which neutrophils continue to accumulate (Fig. 46). As the pustule ages, the cellular walls gradually break in the center of the pustule so that

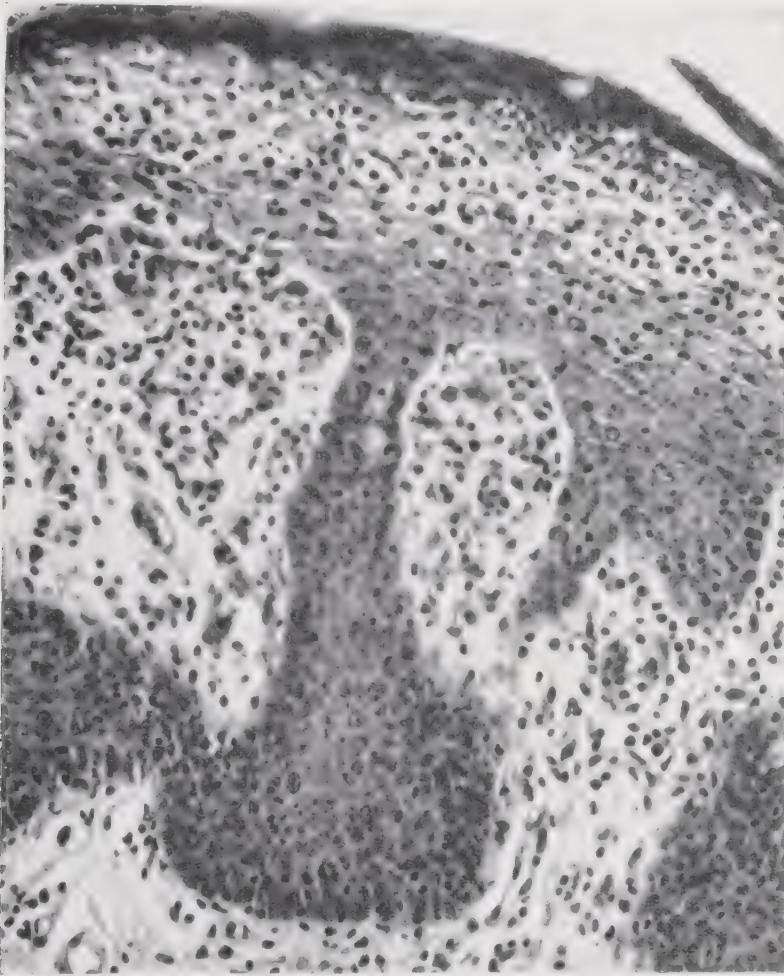


FIG. 46. Acrodermatitis continua of Hallopeau. There is acanthosis with elongation of the rete ridges. The upper stratum malpighii contains a spongiform pustule: the cellular walls of the edematous squamous cells form a sponge-like network in the interstices of which neutrophils have accumulated. ($\times 300$)

a large cavity forms. At the periphery of the pustule, however, the network persists for a much longer time.

Differential Diagnosis. The spongiform pustule of Kogoj represents a striking histologic lesion and is characteristic of acrodermatitis continua. However, it is not diagnostic of that disease since it occurs also in three other diseases: impetigo herpetiformis, keratosis blennorrhagica and Reiter's disease. Differentiation of these four

diseases may be impossible. However, in impetigo herpetiformis, the infiltrate contains, as a rule, a large number of eosinophils (see below). Older lesions of keratosis blennorrhagica and Reiter's disease often can be differentiated from acrodermatitis continua by the presence of a greatly thickened horny layer (see page 172).

IMPETIGO HERPETIFORMIS

This rare, usually fatal, disease is seen mainly in pregnant women and occasionally in hypoparathyroidism. It is characterized by the presence of pustules set in groups or in circinate arrangement on erythematous patches.

Histopathology. The histologic picture, like that of acrodermatitis continua, is characterized by the presence of the spongiform pustule (Kogoj). (See "Acrodermatitis Continua" for a description of the spongiform pustule.) The dermal infiltrate as well as the pustule contain a conspicuous number of eosinophils (Rost).

Differential Diagnosis. The presence of many eosinophils aids in the differentiation of impetigo herpetiformis from the other three diseases with spongiform pustules: acrodermatitis continua, keratosis blennorrhagica and Reiter's disease. The latter two diseases, in addition, often show conspicuous hyperkeratosis in their older lesions.

PARAPSORIASIS

Parapsoriasis comprises a group of rare dermatoses. Three of the four forms of parapsoriasis are characterized by an asymptomatic maculopapular eruption of slow evolution and marked chronicity. These forms are: parapsoriasis guttata, parapsoriasis lichenoides (parakeratosis variegata) and parapsoriasis en plaques. In parapsoriasis guttata, one observes, especially on the trunk, numerous papules which may or may not be covered with fine scales. In parapsoriasis lichenoides, papules generally are distributed in a netlike arrangement. In parapsoriasis en plaques, well-defined patches and plaques of various size and shape occur. The fourth form of parapsoriasis, parapsoriasis varioliformis of Habermann, also called pityriasis lichenoides et varioliformis acuta, differs from the previously mentioned forms by running an acute course terminating in from a few weeks to several months. The eruption consists of vesicles, papules and papulonecrotic lesions terminating in varioliform scars.

Histopathology. None of the four forms of parapsoriasis shows a diagnostic histologic picture. Parapsoriasis guttata, parapsoriasis lichenoides and parapsoriasis en plaques show the histologic picture of chronic dermatitis, while parapsoriasis varioliformis shows an acute inflammatory process with foci of necrosis.

PARAPSORIASIS GUTTATA. The histologic picture is that of a chronic dermatitis. Parakeratosis is usually quite evident. In some cases, there is considerable resemblance to either seborrheic dermatitis or psoriasis. Even Munro micro-abscesses may be found (McCarthy). Montgomery stresses as a point of differentiation from psoriasis the presence of spotted areas of liquefaction degeneration in the basal-cell layer.

PARAPSORIASIS LICHENOIDES (PARAKERATOSIS VARIEGATA). McCarthy denies the existence of this variety and believes that cases reported as such are either early mycosis fungoides, atypical lichen planus or parapsoriasis guttata. On the other hand, Montgomery and Burkhart and Carol, Prakken and Stigter regard it as a definite, though very rare, entity. The histologic changes are those of a chronic dermatitis. There may be atrophy of the epidermis (Montgomery).

PARAPSORIASIS EN PLAQUES. The histologic picture is that of a chronic dermatitis. There is usually little or no parakeratosis. There may be edema of the upper dermis (Montgomery).

PARAPSORIASIS VARIOLIFORMIS OF HABERMANN. This disorder is regarded by some as a subvariety of parapsoriasis guttata (Montgomery) and by others as a separate entity within the parapsoriasis group. According to Miescher, cases intermediary between parapsoriasis guttata and parapsoriasis varioliformis occur. The histologic changes consist of a dense, acute inflammatory infiltrate in the upper dermis pressing against and invading the epidermis. The epidermis shows in the early lesion hydropic degeneration of the squamous cells and multiple intra-epidermal vesicles. In the late lesion, one finds destruction of the epidermis with formation of a necrotic crust (Senear and Oliver; Robinson).

Differential Diagnosis. Early mycosis fungoides may imitate, in its clinical appearance, parapsoriasis lichenoides and parapsoriasis en plaques. Since the histologic picture of early mycosis fungoides, just like that of parapsoriasis lichenoides and parapsoriasis en plaques, may be one of nonspecific chronic dermatitis, every case in which a diagnosis of parapsoriasis lichenoides or parapsoriasis en plaques has been made should be regarded as one of possible mycosis fungoides and further biopsy studies should be done at intervals (Keil).

PITYRIASIS ROSEA

Pityriasis rosea is a self-limited disorder lasting from 4 to 7 weeks. The lesions, which are found chiefly on the trunk, consist of round or oval, salmon-colored patches with peripherally attached, thin, cigarette-paper-like scales.

Histopathology. The histologic picture is that of a nonspecific chronic dermatitis (see page 70). The infiltrate in the upper dermis consists of lymphocytes and some neutrophils. The epidermis shows slight acanthosis with spongiosis and intracellular edema. Occasionally, the edema may result in the formation of a few small vesicles within the stratum malpighii or beneath the horny layer. Lympho-

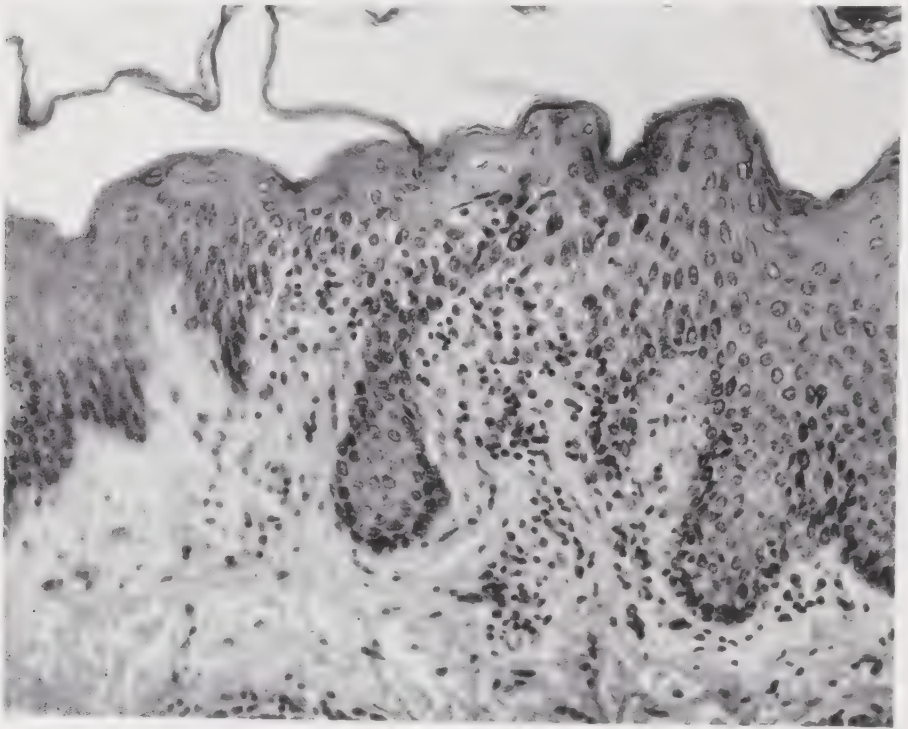


FIG. 47. **Pityriasis rosea.** The epidermis shows spongiosis and is invaded by lymphocytes. The upper dermis shows a rather marked inflammatory infiltrate. ($\times 200$)

cytes are scattered through the epidermis (Fig. 47). A moderate degree of parakeratosis is usually found.

LICHEN PLANUS

Lichen planus is a subacute or a chronic dermatosis characterized by small, flat-topped, shiny, angular, violaceous papules. As a rule, itching is severe. The disease usually is limited to a few areas, but may be generalized. The oral mucosa is involved frequently. In rare instances, bullae top the lesions of lichen planus (bullous lichen planus). In old cases, one may find considerable verrucous hyperplasia (hypertrophic lichen planus).

Lichen planopilaris (lichen planus follicularis) designates lichen planus with follicular arrangement of some or all of the lesions. This

type of lichen planus frequently affects the scalp. Loss of hair ensues in the involved areas leading, in the scalp, to irregularly shaped patches of usually permanent alopecia. Lichen spinulosus et folliculitis decalvans of Little and lichen planus et acuminatus atrophicans of Feldman are terms formerly applied to lichen planopilaris.

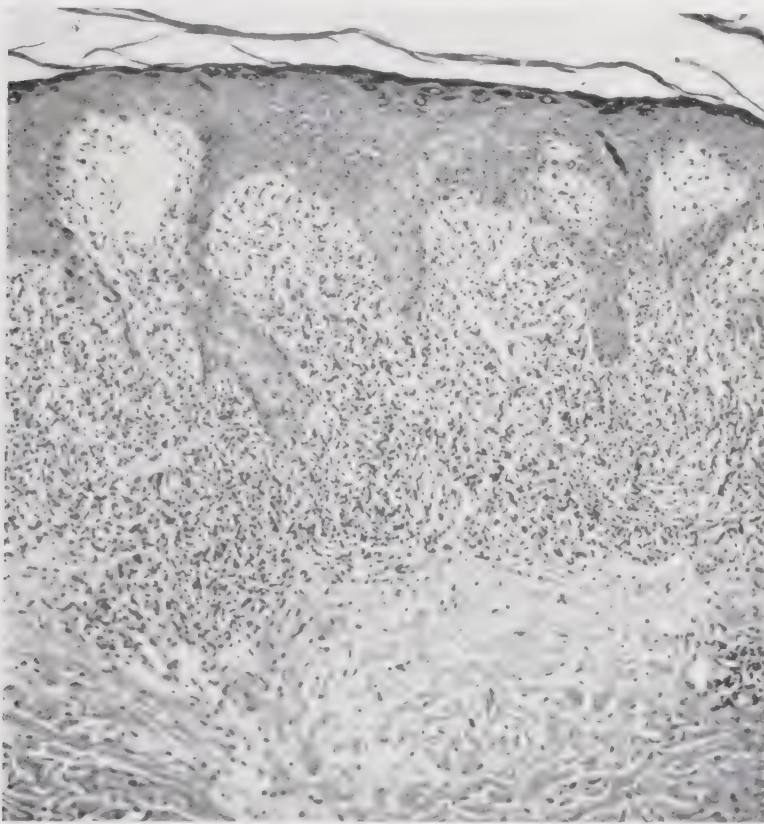


FIG. 48. Lichen planus, early lesion. The granular layer is prominent. There is acanthosis with irregular lengthening of the rete ridges. The rete ridge in the center has a triangular, "saw-tooth" appearance which is quite characteristic of lichen planus. The basal layer has been destroyed by the inflammatory infiltrate. The infiltrate consists almost entirely of lymphocytes. It is bandlike, "hugs" the epidermis and is sharply demarcated at its lower border. ($\times 100$)

Histopathology. Lichen planus shows (1) hyperkeratosis, (2) increase in thickness of the stratum granulosum, (3) irregular acanthosis, (4) destruction of the basal layer and (5) a bandlike infiltrate pressing against and invading into the epidermis (Fig. 48).

The horny layer is moderately thickened and—important for the diagnosis—never contains any parakeratotic cells. The granular layer often shows considerable hypertrophy, out of proportion to the hy-

pertrophy of the horny layer. The keratohyaline granules in the granular cells are more abundant and coarser than normally observed. The acanthosis affects the stratum malpighii as well as the rete ridges. The rete ridges often show irregular lengthening; some of the rete ridges are pointed at their lower end, which gives them a "saw-tooth" appearance. The basal layer in early lesions is visualized poorly because of the invading inflammatory infiltrate and in fully developed

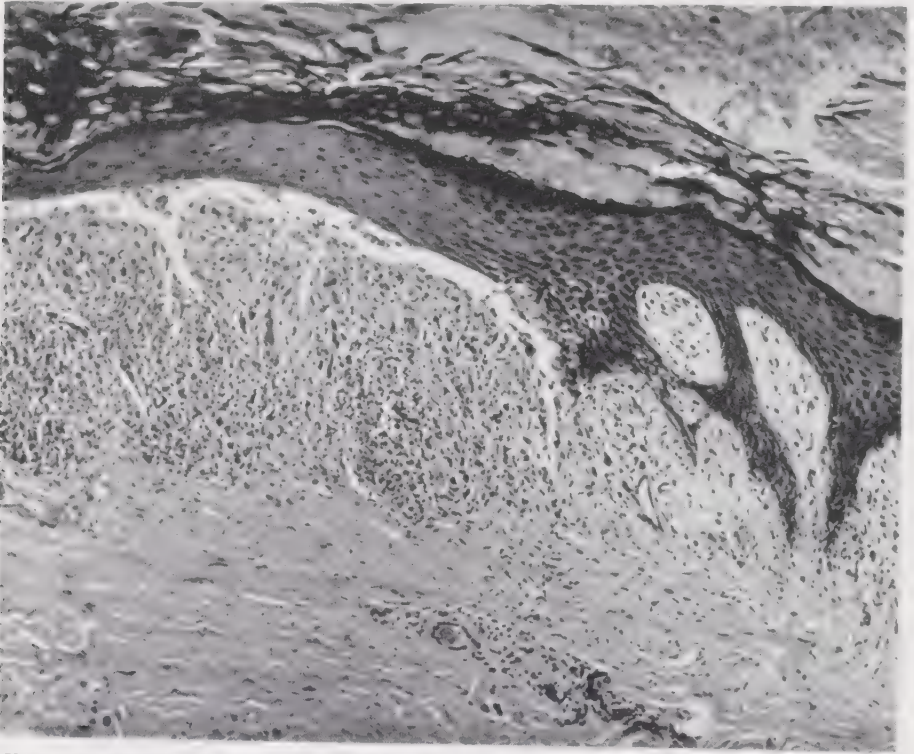


FIG. 49. Lichen planus, bullous lesion. Extensive separation of the epidermis from the dermis has taken place. ($\times 100$)

lesions often is almost completely absent, having been destroyed by the infiltrate.

The infiltrate in the upper dermis is bandlike and quite sharply demarcated at its lower border, "hugs" the epidermis and invades the lower epidermis so that the outline between epidermis and dermis becomes hazy (moth-eaten). The infiltrate is composed almost entirely of lymphocytes with a few histiocytes interspersed. In early lesions, however, some polymorphonuclear leukocytes are usually present (Winer and Levitt). Plasma cells are few in number and eosinophils are absent.

Occasionally, one sees small areas of separation between the epidermis and the dermis (hole formation). In some instances, the separation increases to such extent that subepidermal bullae form: lichen

planus bullosus (Fig. 49). These bullae form because of the destruction of the basal cells (see "Classification of Bullae," page 66).

In older lesions, the infiltrate decreases in density and the number of histiocytes and fibroblasts increases. Melanophores are present in the upper dermis, often in considerable number, since, as a result of the damage to the basal layer, the melanocytes of the basal layer are



FIG. 50. Lichen planopilaris. There is a dilated follicle filled with a keratotic plug. At the lower pole of the follicle is a dense lymphocytic infiltrate. In addition, there is a bandlike infiltrate beneath the epidermis. ($\times 50$)

incapable of storing and metabolizing melanin properly ("symptomatic incontinentia pigmenti," see Glossary). In the late stage, the epidermis may become either atrophic or thickened with considerable hyperkeratosis. In the latter case, one speaks of hypertrophic lichen planus.

Oral lesions have the same histologic aspect as the cutaneous lesions. There may be no granular layer, as in the normal oral mucosa. Frequently, however, a granular layer is present.

LICHEN PLANOPILARIS (LICHEN PLANUS FOLLICULARIS). In lichen planopilaris, in addition to the subepidermal infiltrate, one finds a dense lymphocytic infiltrate at the lower pole of the follicle. In older lesions, the hair is obliterated and the follicle dilated and filled with

a keratotic plug (Fig. 50). The pressure of the inflammatory infiltrate against the base of the follicle is the cause of the obliteration of the hair and of the follicular hyperkeratosis (Feldman; Sachs and DeOreo).

Differential Diagnosis. The differential diagnosis between leukoplakia and lichen planus of the lips or the mouth occasionally may cause difficulties, clinically as well as histologically. Both diseases show hyperkeratosis, acanthosis, irregular proliferation of the rete ridges and an inflammatory infiltrate close to the epidermis, and in both diseases a granular layer, normally absent, may be present. Thorough study of the epidermis, however, usually reveals in leukoplakia some atypicality of the rete cells. Furthermore, the inflammatory infiltrate in leukoplakia, as a rule, contains a considerable number of plasma cells.

LICHEN NITIDUS

Lichen nitidus is characterized by indolent, small, pink or flesh-colored, shiny papules which occur in groups but do not coalesce.

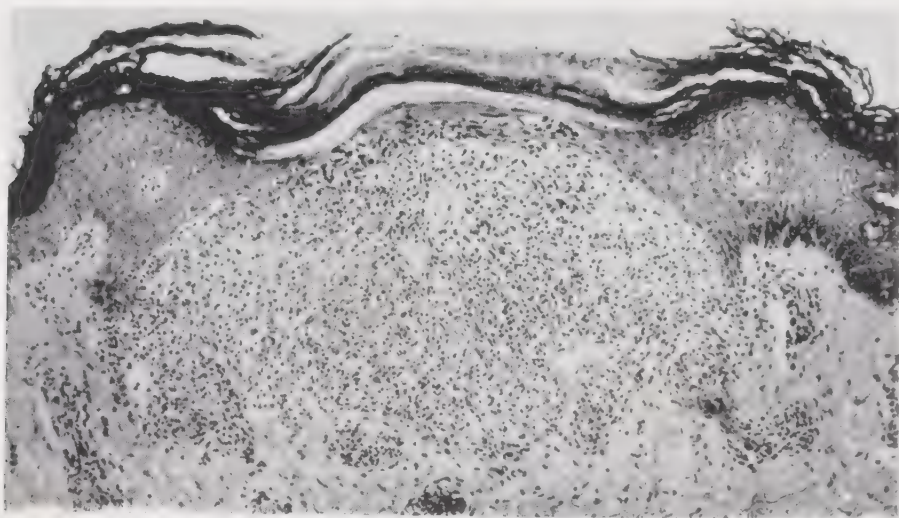


FIG. 51. **Lichen nitidus.** A circumscribed nest of cells lies in close contact with the epidermis. The infiltrate consists of lymphocytes, histiocytes and epithelioid cells. The epidermis above the infiltrate is flattened. ($\times 100$)

Their sites of predilection are the penis and the flexor surfaces of the forearms.

Histopathology. The lesions of lichen nitidus consist of circumscribed nests of cells which appear as if glued to the lower border of the epidermis. The infiltrate consists mainly of lymphocytes and histiocytes. Some of the latter have the appearance of epithelioid cells

(Fig. 51). A few Langhans giant cells are often present. Plasma cells are absent, and there is no caseation necrosis. The epidermis above the infiltrate is flattened and shows disintegration of the basal layer. At the margin, rete ridges tend to grow downward and seem to clutch the infiltrate in the manner of a claw clutching a ball.

The cause of the disease is not known. Ellis and Hill regard lichen nitidus as closely related to lichen planus, because they found that the two diseases may occur together and histologic sections obtained from patients with lichen planus may show lichen-nitidus-like lesions.

LICHEN STRIATUS

Lichen striatus is an uncommon eruption which, as a rule, occurs in children. It manifests itself, usually on the extremities, as a long band composed of small lichenoid papules. The eruption appears suddenly and involutes within a few weeks or months. Itching is absent.

Histopathology. The histologic changes are similar to those of neurodermatitis circumscripta. In some cases, the chronic inflammatory infiltrate is more markedly perivascular than in neurodermatitis circumscripta and surrounds the vessels of the upper dermis as densely packed mantles (Senear and Caro; Pinkus).

PITYRIASIS RUBRA PILARIS

The primary lesions are reddish follicular papules. They gradually coalesce to form thickened, dry, scaly, red plaques. Ultimately, most of the body surface may be affected. Even at that late stage, however, follicular papules usually can be detected, especially on the dorsa of the fingers.

Histopathology. The essential pathologic process is follicular hyperkeratosis. In addition, there is diffuse hyperkeratosis with spotted parakeratosis. The epidermis shows irregular acanthosis, usually of mild degree. There often is liquefaction degeneration of the basal cells (Brunsting and Sheard). In the upper dermis, a mild chronic inflammatory infiltrate is observed around the blood vessels.

Differential Diagnosis. For a differential diagnosis from phrynodema (vitamin-A deficiency), see page 286.

GRANULOMA FACIALE (EOSINOPHILIC GRANULOMA OF THE FACE)

This disorder, only recently established as a disease entity, consists of soft, purplish, slowly growing and asymptomatic patches limited to the face. Except for prominence of the follicular openings, the surface of the skin appears normal.

Histopathology. A dense, granulomatous infiltrate is located mainly in the upper half of the dermis (Fig. 52). Quite characteristically, the infiltrate does not invade the epidermis or the pilosebaceous appendages but is separated from them by a narrow zone of normal collagen. The pilosebaceous appendages are well preserved. Two stages can be differentiated in the development of the

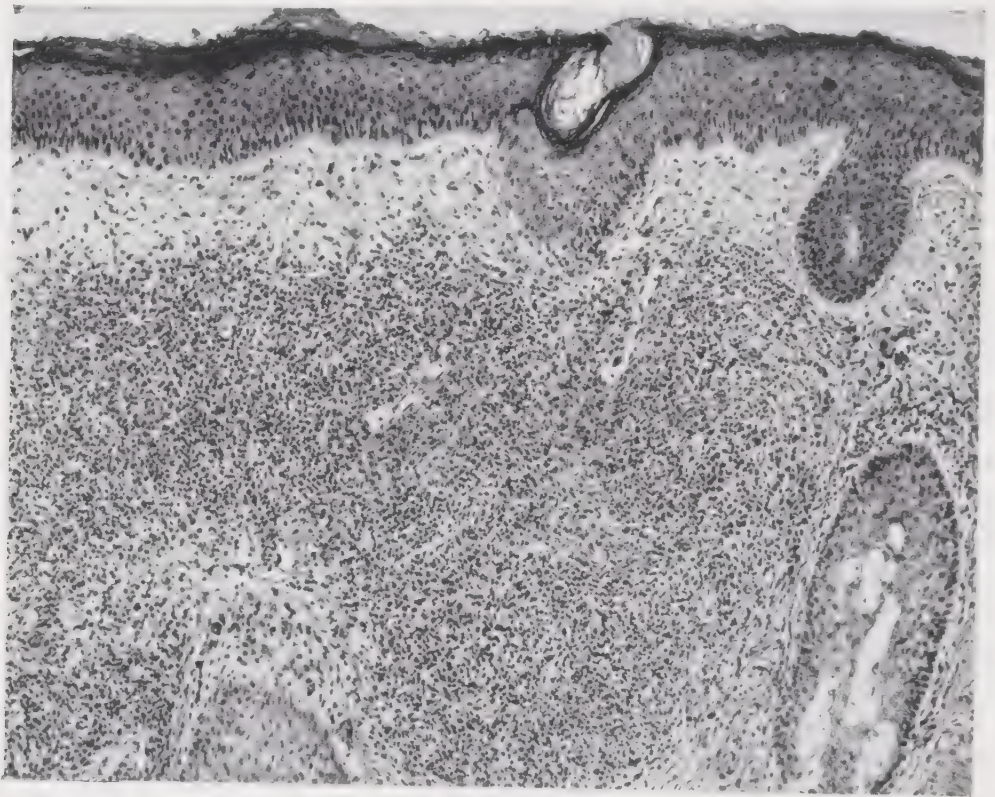


FIG. 52. **Granuloma faciale.** A dense infiltrate containing many eosinophils is present in the dermis. The infiltrate does not invade the epidermis or the sebaceous gland shown on the right but is separated from them by a zone of normal collagen. ($\times 100$)

infiltrate, an early "leukocytic" and a late "fibrotic" stage. The two stages may occur together in the same lesion.

In the early "leukocytic" stage, eosinophils predominate, but neutrophils and histiocytes are found in large number and, in addition, a few lymphocytes, plasma cells and mast cells. The infiltrate thus has a polymorphous appearance. The capillaries are dilated and surrounded by degenerated collagen (Fig. 53). In some cases, considerable amounts of hemosiderin are present in the upper dermis within and outside of histiocytes (Lever, Lane, Downing and Spangler). The presence of foam cells has been described in one case (Lever).

In the late "fibrotic" stage, the infiltrate is broken up into variously sized patches by strands of collagen. The number of eosinophils and neutrophils is greatly reduced, and plasma cells, lymphocytes and fibroblasts predominate. The capillaries often have fibrotic walls.

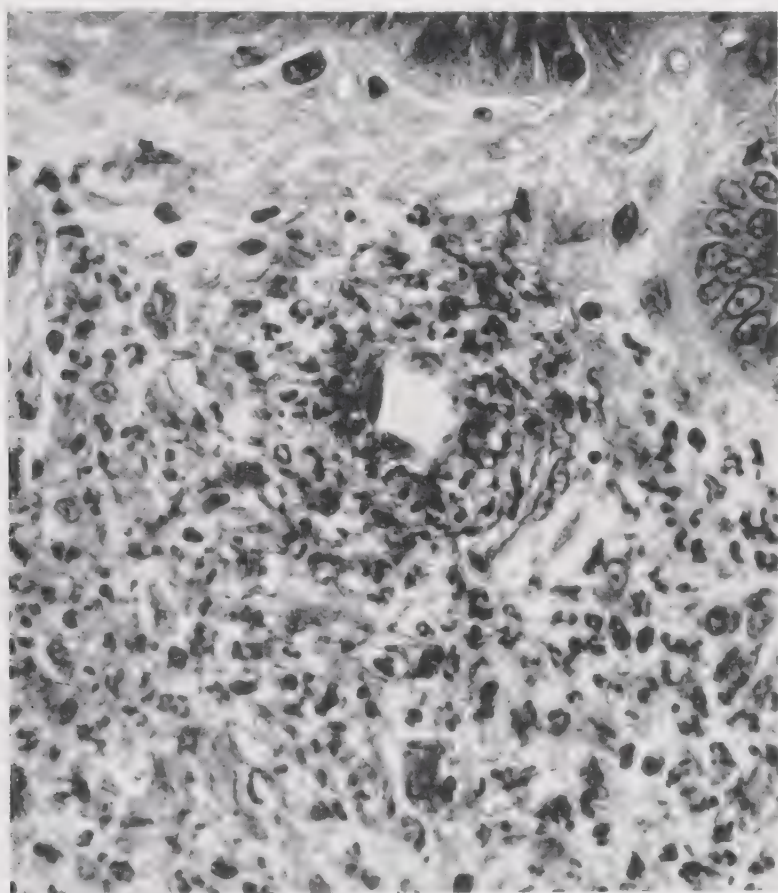


FIG. 53. Granuloma faciale. There is a granulomatous infiltrate which is densest around a dilated capillary. Two types of cells, eosinophils and histiocytes, predominate. ($\times 400$)

Differential Diagnosis. The arrangement and the composition of the infiltrate in granuloma faciale result in a diagnostic histologic picture with no resemblance to that of eosinophilic granuloma with which the disease was at first confused (Lever). Although eosinophilic granuloma, which represents an abortive form of Hand-Schüller-Christian disease (see page 265), also contains many eosinophils and histiocytes, its histologic appearance differs from that of granuloma faciale by the following characteristics: the histiocytes are much larger and possess abundant acidophilic cytoplasm, the eosinophils lie in patchy aggregates and the infiltrate usually invades and destroys

the epidermis (Lever and Leeper). For a differentiation from erythema elevatum diutinum, see below.

ERYTHEMA ELEVATUM DIUTINUM

This rare disorder shows persistent, red to purple nodules with some tendency to grouping about the joints, especially on the dorsa of the hands, the wrists and the elbows. The nodules at first are soft but later, due to fibrous transformation, become hard.

Histopathology. Erythema elevatum diutinum has a fairly diagnostic histologic picture which was first described by Weidman and Besancon, and then by Ketron and by Weiss as well as by others. The disease described in 1894 by Crocker and Williams as erythema elevatum diutinum of the Bury type is now widely regarded as a variant or late stage of granuloma annulare (Haber and Russell).

Erythema elevatum diutinum, in its early stage, shows a dense, predominantly perivascular infiltrate composed largely of neutrophils intermingled with some lymphocytes and histiocytes. In most cases, a peculiar hyaline degeneration of the reticulum fibers around the capillaries has been observed. This degeneration has been referred to by Weidman and Besancon and by Ketron as formation of "toxic hyalin." This toxic hyalin has a smooth, glassy appearance and stains intensely pink with eosin.

In the late, fibrous stage, the cellular infiltrate is much less pronounced and extensive fibrosis is present. The capillaries may still show their mantle of toxic hyalin or may merely show fibrous thickening (Ketron).

Differential Diagnosis. The histologic appearance of erythema elevatum diutinum differs from that of granuloma faciale by the predominance of neutrophils rather than eosinophils, the absence of a zone of normal collagen beneath the epidermis and the presence of "toxic hyalin" about the capillaries.

GRANULOMA ANNULARE

The lesions, which are found most commonly on the hands and the feet, consist of small, firm, pale-red nodules which tend to be grouped in a ringlike or circinate arrangement. The disease is chronic and free of subjective symptoms.

Histopathology. Histologically, granuloma annulare is characterized by focal degeneration of the collagen in the dermis, deposits of mucin between the degenerated collagenous bundles and reactive inflammation and fibrosis. The degeneration of collagen within the foci may be complete or incomplete. Some cases show foci of both complete and incomplete degeneration and others show only one



FIG. 54. **Granuloma annulare.** There is a large, sharply circumscribed focus of complete degeneration of the collagen. It is surrounded by histiocytes, fibroblasts and lymphocytes in radial arrangement. ($\times 50$)

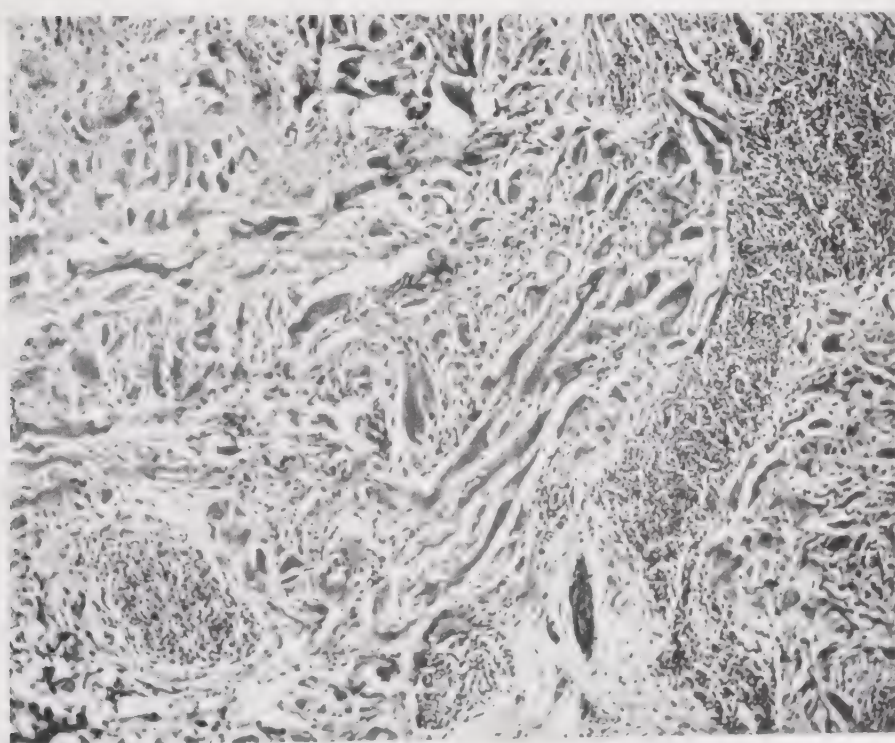


FIG. 55. **Granuloma annulare.** In the left upper quadrant is an ill-defined area of incomplete degeneration of collagen. Some of the collagen bundles are in various stages of degeneration; others appear normal. Note the disorderly arrangement of the collagen bundles. Peripheral to the area of collagen degeneration, a marked perivascular inflammatory infiltrate is present. ($\times 100$)

large focus of complete collagen degeneration. In the majority of cases, however, one finds multiple foci of incomplete degeneration without any foci of complete degeneration.

In foci of complete degeneration, one finds a sharply demarcated area of coagulation necrosis surrounded by an infiltrate of histiocytes, fibroblasts and lymphocytes in a radial arrangement (Fig. 54).

In foci of incomplete degeneration, one finds ill-defined areas in which collagen fibers are found in various stages of degeneration ranging from mild homogenization and fragmentation to granular degeneration and coagulation necrosis. A considerable amount of the collagen in such areas may appear normal. Lymphocytes, histiocytes and fibroblasts infiltrate between the partially degenerated collagen fibers and new collagen is being laid down. Thus, the affected areas of the dermis present a completely disorderly arrangement of the collagen bundles (Fig. 55).

In both types of collagen degeneration, though more frequently in areas of incomplete degeneration, fine threads and granules of mucin are deposited between the degenerated collagen bundles. The mucin stains light blue with routine stains and red when Best's mucicarmin stain is used. (See Plate I.)

In areas of collagen degeneration, the elastic tissue shows fragmentation and may be largely destroyed. In some areas, there may even be greater destruction of elastic than of connective tissue. A moderate or even considerable amount of lymphocytic infiltration is found around the blood vessels outside the areas of degeneration. The walls of the blood vessels show no pathologic changes, however, except occasional mild endothelial proliferation. In some cases, a few giant cells of the foreign-body type are present. They usually are situated near the periphery of the infiltrate and are not associated with any zone of necrosis (Prunty and Montgomery).

Differential Diagnosis. The type of granuloma annulare showing multiple foci of incomplete collagen degeneration may greatly resemble necrobiosis lipoidica which shows this same pattern of collagen degeneration (see page 269). However, necrobiosis lipoidica differs from granuloma annulare by the presence of vascular changes, of lipid material and of many foreign-body giant cells and by the absence of mucin.

The type of granuloma annulare showing one or several large foci of complete collagen degeneration may be almost indistinguishable from the subcutaneous nodes of rheumatoid arthritis (see below). However, in the nodes of rheumatoid arthritis, the areas of degeneration are usually larger, they are more deeply located in the dermis or even in the subcutis, and they are encircled by a less varied cellular

reaction, mainly histiocytes and fibroblasts, while in granuloma annulare there are, in addition, many lymphocytes (Bowers).

SUBCUTANEOUS NODULES OF RHEUMATIC FEVER AND RHEUMATOID ARTHRITIS

In both rheumatic fever and rheumatoid arthritis, small firm nodules may form in the subcutaneous tissue. The commonest sites

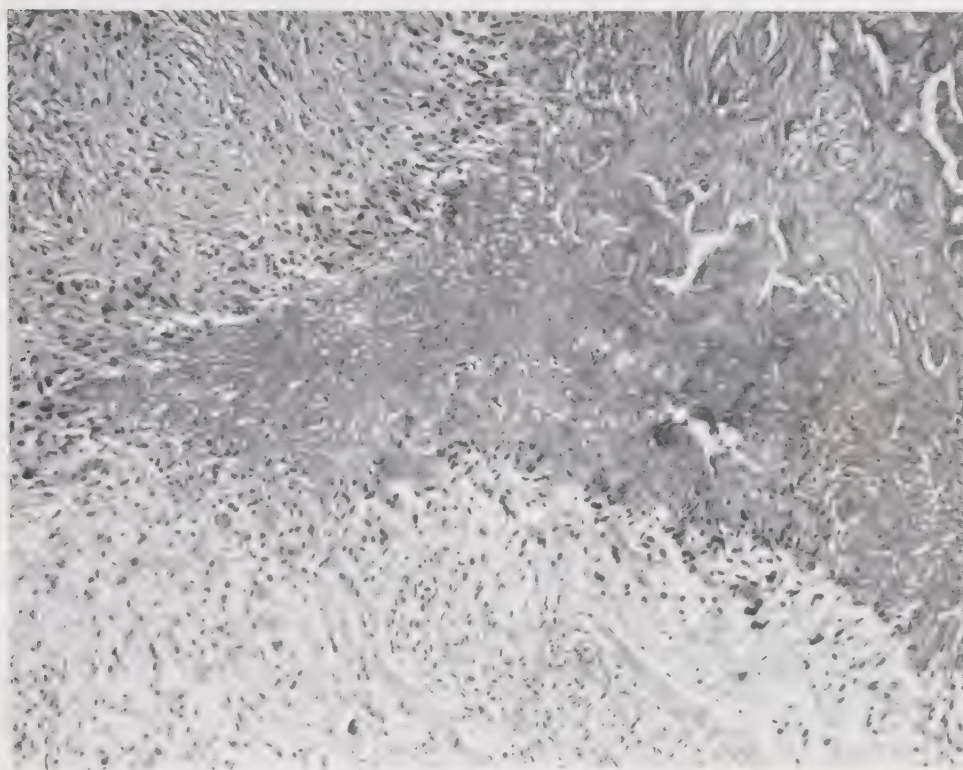


FIG. 56. Subcutaneous nodule of rheumatoid arthritis. There is a large central zone of necrosis surrounded by histiocytes in palisade arrangement. ($\times 100$)

are about the elbows, the knees and the ankles. Their size varies from a few millimeters to 2 cm.

Histopathology. The subcutaneous nodules found in these two diseases are similar in many of their pathologic features. In both diseases they are composed of three reasonably well-defined zones: (1) a central zone, or zone of necrosis, (2) an intermediate zone, comprising proliferating histiocytic cells and (3) a peripheral zone, consisting of chronic inflammatory cells (Bennett, Zeller and Bauer). However, exudative changes prevail in the nodules of rheumatic fever; proliferative and necrotic changes in those of rheumatoid arthritis.

In rheumatic fever, the central zone shows "fibrinoid degeneration." (For a discussion of fibrinoid degeneration, see "Acute Systemic Lupus Erythematosus," page 297.) The intermediate zone is composed of edematous collagen infiltrated with inflammatory cells, including many large mononuclear cells (histiocytes) which resemble the predominant cells of myocardial Aschoff nodules.

In rheumatoid arthritis, the central zone shows necrosis of all pre-existing collagen, and the intermediate zone distinct palisading of histiocytes and fibroblasts around the central zone of necrosis (Fig. 56).

Differential Diagnosis. For differentiation of the nodules of rheumatoid arthritis from granuloma annulare, see "Granuloma Annulare," page 116.

ACRODERMATITIS CHRONICA ATROPHICANS

This condition affects the extremities. The skin presents a bluish red or a brownish, atrophic, wrinkled appearance. Fine scaling is usually present. Because of decrease in the amount of subcutaneous fat, the subcutaneous veins are clearly visible. In some cases, bandlike areas of fibrosis, resembling scleroderma, and fibrous nodules are observed, especially along the ulna as "ulnar bands" and along the tibia.

Histopathology. The histologic picture is characteristic. One observes mild to moderate hyperkeratosis and atrophy of the epidermis, with absence of the rete ridges. Just beneath the epidermis, there is a narrow zone of connective tissue separating a dense band of inflammatory infiltrate from the epidermis. In addition to this bandlike infiltrate, one finds scattered areas of inflammatory infiltration throughout the dermis, particularly around the blood vessels. The infiltrate is composed predominantly of lymphocytes, but also contains histiocytes. Chromatophores laden with melanin or hemosiderin may be present. The entire dermis shows interstitial edema and atrophy of the collagenous bundles. The atrophy results in a gradual decrease of the dermis to a half or a quarter of its normal thickness (Fig. 57).

The sebaceous glands and the hairs undergo atrophy early in the disease and usually are entirely absent. However, the sweat glands are, as a rule, preserved. Because of the thinness of the dermis, they lie unusually close to the epidermis. The blood vessels are dilated and may show endothelial proliferation.

The subcutaneous tissue shows decided atrophy. The fat cells vary in size and are irregular in shape. Foci of inflammatory infiltration and a varying degree of fibrosis are present.

After many years' duration, an atrophic stage may be reached in which the findings are no longer diagnostic, since one sees merely an atrophic epidermis and an atrophic, fibrotic dermis without inflammatory infiltrate.

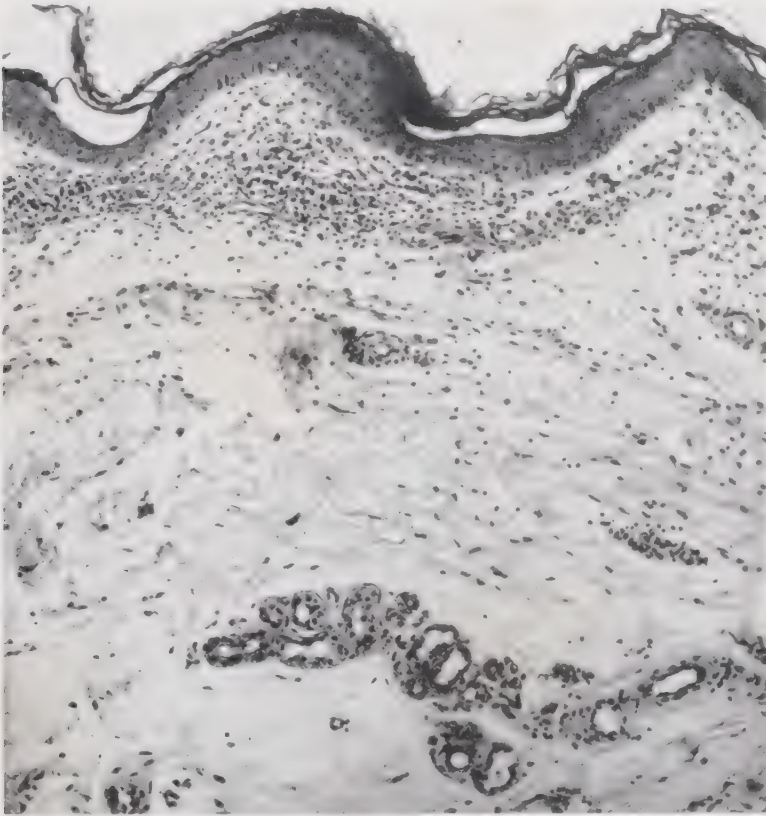


FIG. 57. *Acrodermatitis chronica atrophicans*. There is atrophy of the stratum malpighii. A bandlike infiltrate is separated from the epidermis by a narrow zone of normal collagen. The dermis shows interstitial edema and atrophy of the collagen bundles. Because of this atrophy, the thickness of the dermis is markedly decreased and the sweat glands lie unusually close to the epidermis. ($\times 100$)

The bandlike areas of fibrosis resembling scleroderma and the fibrous nodules which may be seen in *acrodermatitis chronica atrophicans* usually show nothing more than dense fibrosis. Occasionally, however, the bandlike areas show a histologic picture indistinguishable from that of scleroderma.

RADIODERMATITIS

An early (acute) and late (chronic) stage of radiodermatitis are recognized. The early stage occurs within a few days after adminis-

tration of a massive dose of roentgen rays or radium. At first, there is erythema, which is followed by desquamation and pigmentation. If the dose administered is sufficiently large, ulceration will ensue. The late (chronic) stage of radiodermatitis occurs from a few months



FIG. 58. **Late radiodermatitis.** The epidermis shows acanthosis and downward growth around a telangiectatic blood vessel. Many irregularly dilated lymphatics are located directly beneath the epidermis. The collagen shows degeneration. ($\times 100$)

to several years after the administration of large amounts of roentgen rays or radium. The skin shows atrophy with interspersed areas of hyperkeratosis, irregular hyperpigmentation, telangiectases and loss of hair. Ulceration may be present. The hyperkeratoses may develop into squamous-cell carcinoma.

Histopathology of Early (Acute) Radiodermatitis. The cells of the epidermis, particularly those of the basal layer, are hydropic and their nuclei show pyknosis. The epithelial cells of the hair follicles, the sebaceous glands and the sweat glands may show similar degenerative

changes. An inflammatory infiltrate is seen throughout the dermis, especially about the appendages. The blood vessels are dilated and reveal edema of their walls and endothelial proliferation. The collagen bundles show edema and homogenization. In severe cases, the

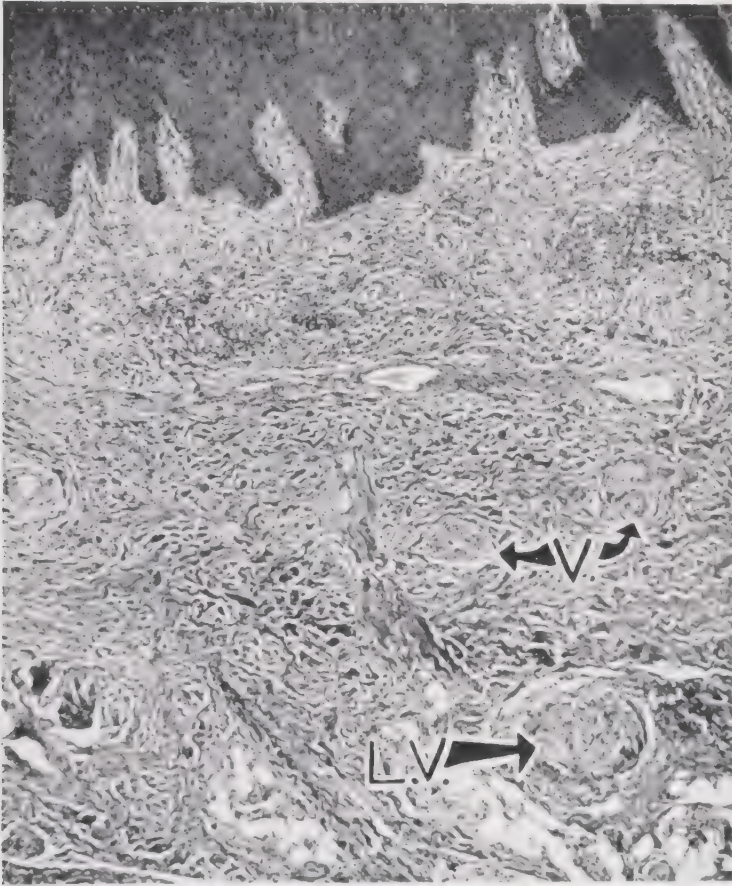


FIG. 59. **Late radiodermatitis.** The vessels (V.) show fibrotic thickening of their walls. A large vessel (L.V.) at the junction of dermis and subcutis shows thrombosis. The collagenous bundles of the dermis appear sclerotic. ($\times 50$)

epidermis and the upper dermis undergo necrosis. The area of necrosis is invaded and surrounded by polymorphonuclear leukocytes.

Histopathology of Late (Chronic) Radiodermatitis. The epidermis is irregular, showing atrophy in some areas and acanthosis with hyperkeratosis in others. The rete cells frequently show atypicality, such as disorderly arrangement, individual cell dyskeratosis and an increased number of mitotic figures. Thus the changes may resemble those of Bowen's disease (intra-epidermal squamous-cell carcinoma). In addition, there often is irregular downward growth of the epidermis. The

rete ridges may grow around telangiectatic vessels, which may thus become completely enclosed in the epidermis (Fig. 58).

In the dermis, the collagenous fibers are swollen and sclerotic. In some areas, they are broken apart and stain basophilic. Formation of new, young connective tissue is found throughout the dermis, but especially around the blood vessels. Directly beneath the epidermis, one often sees numerous irregularly dilated lymphatics as well as lymphedema.

However, the fundamental pathologic change is that of fibrotic thickening of the walls of the vessels in the deeper portions of the dermis, leading to occlusive changes in the lumina (Fig. 59). Some of the vessels show thrombosis and recanalization. The vessels nearest to the epidermis may show telangiectasia.

Hair follicles and sebaceous glands are absent, but the sweat glands usually are preserved, except in areas of third-degree injury. The elastic tissue is, as a rule, less damaged than the collagenous tissue—at least in milder degrees of radiodermatitis. In severe reactions, it is destroyed. With Foot's reticulum stain, the reticulum fibers are seen to be increased throughout the dermis, wherever there is formation of young connective tissue, but especially around blood vessels.

In severe cases of chronic radiodermatitis, ulceration occurs. The deep-lying, large blood vessels beneath the ulcers, as a rule, show complete obliteration.

The above-described epidermal changes of dyskeratosis and intra-epidermal carcinoma frequently lead on to invasive squamous-cell carcinoma. A fairly large percentage of them are of high (grade IV) malignancy and of the spindle-celled variety (see page 333). In rare instances, basal-cell epitheliomas develop in areas of radiodermatitis (Anderson and Anderson) (see under "Basal-Cell Epithelioma," page 370). The occurrence of sarcoma, on the other hand, is not fully established. Such instances have been reported (Blom-Ides; Gentile), but always with the reservation that the diagnosis of spindle-celled squamous-cell carcinoma could not be ruled out conclusively because this differentiation may be nearly impossible (see page 410). A point in favor of their being carcinoma is the fact that they are, in contrast to fibrosarcoma, radiosensitive (Blom-Ides).

SOLAR DERMATITIS

Solar dermatitis may occur as erythematous, urticarial, papular or vesicular lesions in areas exposed to the sun. The erythematous lesions may resemble lupus erythematosus in their clinical appearance by showing a livid red color and slight induration.

Histopathology. The histologic appearance usually is that of a nonspecific chronic dermatitis (see page 70). However, the erythematous lesions frequently present areas of liquefaction degeneration of the basal layer; and edema together with a patchy, predominantly lymphocytic infiltrate in the upper dermis. Differentiation from lupus erythematosus may then be impossible. However, in some cases of solar dermatitis, a moderate number of eosinophils is present in the infiltrate. Since eosinophils are generally not observed in lupus erythematosus, their presence aids greatly in the differentiation of the two diseases (Lamb).

HIDROCYSTOMA

This condition is characterized by the presence on the face of numerous clear, tense, deep-seated vesicles varying in size from a few millimeters to 1 centimeter.

Histopathology. On histologic examination, one observes in the dermis large cystic cavities lined by epithelial cells which usually are arranged in two layers. Small papillary projections into the lumina of the cysts have been described (Kenedy and Lehner).

Most authors regard the cysts as caused by retention of sweat in the dermal portion of eccrine sweat ducts. However, Kenedy and Lehner believe that the cysts are not merely the result of retention of sweat and passive dilatation of the excretory ducts but are due to a proliferation of the excretory duct epithelium, which leads to occlusion of the ducts.

ACNE VULGARIS

Acne vulgaris, a disease occurring predominantly in puberty, affects the face, the upper chest and the upper back. The primary lesion is the comedo. As a foreign-body reaction to the comedo and due to secondary infection, follicular papules and pustules and subcutaneous abscesses may occur.

Histopathology. Histologically, acne vulgaris represents a perifolliculitis occurring around a comedo. Comedones are composed of sebum and keratotic as well as parakeratotic cells and are located in the pilosebaceous follicles.

In the early acne lesion, one finds an infiltrate of lymphocytes and plasma cells around a comedo-filled pilosebaceous follicle, together with atrophy and fragmentation of sebaceous glands. The atrophy and the fragmentation of sebaceous glands probably are due to the stasis and the pressure caused by the comedo within the follicle. The fragmentation of sebaceous glands, in turn, causes an inflammatory reaction (Lynch). Occasionally, foreign-body giant cells are found in

the infiltrate, but there is no evidence of tuberculoid reaction. At a later stage, histiocytes and fibroblasts appear and fibrosis occurs.

In lesions in which secondary bacterial infection is present, one finds disintegration of the follicle and abscess formation. Foreign-body giant cells are then frequently found around the remnants of the follicle.

ACNE VARIOLIFORMIS (ACNE NECROTICA MILIARIS)

Acne varioliformis is characterized by the presence of small, indolent papules and pustules along the frontal hairline. The lesions undergo central necrosis and tend to heal with pitted scars.

Acne necrotica miliaris of the scalp is a diminutive variant of acne varioliformis. Because of the superficial location of the necrosis, no hair loss ensues.

Histopathology. The histologic changes of acne necrotica are similar to those of acne vulgaris except that the perifolliculitis is more limited in extent and almost invariably results in central necrosis. Blood vessels adjacent to the necrotic area may be thrombosed. Healing takes place with fibrosis and scar formation.

Acne necrotica miliaris of the scalp shows the same histologic picture as that of acne varioliformis (Montgomery).

ACNE ROSACEA

Acne rosacea occurs in patients with seborrhea and affects the central portion of the face. Two forms of rosacea exist, the papular form and the glandular hyperplastic form. The two forms may occur together. The papular form is characterized by erythema, papules, pustules and telangiectases. The glandular hyperplastic form causes enlargement of the nose, called rhinophyma.

Histopathology. In the papular variety, the infiltrate is either diffusely distributed throughout the dermis or arranged about the hair follicles and the sebaceous glands. As a rule, it is banal in character and composed largely of lymphocytes together with some histiocytes and plasma cells. However, a significant number of patients show, in addition, foci of epithelioid cells and Langhans giant cells, occasionally lying in true tubercle formation, so that the histologic picture is indistinguishable from that of cutaneous tuberculosis. Miescher, who found tuberculoid foci in 80 per cent of 59 patients with acne rosacea, concluded that the rosacea-like tuberculid of Lewandowsky and the papular type of acne rosacea represent the same disease (see page 183). On the other hand, Laymon, who observed tuberculoid structures in only 11 per cent of 138 patients with acne rosacea, does not think that the two diseases are identical:

but he concedes that differentiation of the two diseases by histologic means may be impossible. Additional, but not obligatory, findings in the papular type of rosacea are superficial perifolliculitis, with intrafollicular abscess formation ("pustules"), and dilatation of capillaries. There is no hypertrophy of the sebaceous glands.

In the glandular hyperplastic form, the sebaceous glands are increased in size and number. The orifices of the sebaceous glands are dilated and filled with keratin and sebum. There is an associated hypertrophy of the connective tissue. The blood vessels are dilated. A chronic inflammatory infiltrate is present around the vessels. Perifolliculitis with intrafollicular abscess formation may be observed.

FOX-FORDYCE DISEASE

This disease occurs only in women. It is characterized by an eruption of discrete pruritic papules in the axillae, on the nipples and in the pubic and the perineal regions. It represents a functional disorder of the apocrine glands. Evidence that the disease is related to the apocrine glands is the limitation of the eruption to the areas where apocrine glands occur and the onset of the disease at puberty when the apocrine glands begin to function. Shelley and Hurley have expressed the opinion that Fox-Fordyce disease may be basically a "miliaria apocrina"—in other words, an apocrine-sweat-retention miliaria.

Histopathology. Histologic examination reveals acanthosis with hyperkeratosis. The rete ridges are elongated. A moderate degree of round-cell infiltration is present around the blood vessels in the upper dermis. The appearance thus is that of a chronic dermatitis.

The apocrine glands appear normal (Roxburgh). The statement frequently found in the literature (Nilzén), that in Fox-Fordyce disease the sweat glands are dilated, is due to the fact that many authors have misinterpreted the apocrine glands as dilated sweat glands.

ALOPECIA AREATA

Alopecia areata is characterized by loss of hair in one or several circumscribed areas. There is no visible evidence of inflammation. The scalp is the most common site of lesions. As a rule, there is complete regrowth of hair. In occasional instances, the entire scalp is involved (alopecia totalis), in which case the loss of hair is usually permanent.

Histopathology. The hair follicles and the hair bulbs are greatly reduced in size. The hair bulbs, instead of being deep in the subcutis, are located quite high up in the dermis. The hair follicles contain loose keratin and no hair. In long-standing cases, there is

gross thinning of the dermis, which may be reduced to half its normal thickness (Dillaha and Rothman). In cases of recent onset, a mild to moderately severe inflammatory infiltrate composed of lymphocytes is seen in the deeper dermis about the vessels, the sebaceous glands and the hair follicles, while, in cases of more than 1 year's duration, the inflammatory reaction has subsided (Laymon). The sebaceous and the sweat glands appear normal throughout the course of the disease.

ALOPECIA CICATRISATA (PSEUDOPELADÉ BROCCQ)

In alopecia cicatrisata, one finds scattered through the scalp irregularly shaped patches of alopecia which in the early stage may show perifollicular erythema but in the late stage show smooth atrophy of the skin without any signs of inflammation. The loss of hair is permanent.

Histopathology. In the early stage, one finds a predominantly perifollicular infiltrate composed almost entirely of lymphocytes and a few histiocytes. The infiltrate is present around the upper and the middle thirds of the follicles and spares the lower third. It penetrates into the walls of the follicles and into the sebaceous glands, but not into the lumina of the follicles. Follicular hyperkeratosis may be present (Miescher and Lenggenhager). Gradually, the infiltrate destroys the follicles and the sebaceous glands.

In a late lesion, the epidermis is atrophic and the dermis shows fibrosis. The follicles and the sebaceous glands are absent, but arrectores pilorum and sweat glands are, at least in part, preserved.

Differential Diagnosis. In discoid lupus erythematosus, the inflammatory infiltrate not only is located around hairs and sebaceous glands but also is distributed in a patchy fashion throughout the dermis. In addition, the epidermis shows liquefaction degeneration of the basal-cell layer, hyperkeratosis and more marked keratotic plugging not limited to the follicles. In the late cicatricial stage, a differentiation of the two diseases may be impossible.

Folliculitis decalvans, which represents a folliculitis of the scalp, differs from alopecia cicatrisata by showing formation of intrafollicular abscesses (pustules). The perifollicular infiltrate often contains a fair number of plasma cells which are absent in alopecia cicatrisata (Miescher and Lenggenhager).

PURPURA

Purpura represents a hemorrhage into the skin. Lesions less than 3 mm. in diameter are called petechiae. Larger lesions are called ecchymoses.

Purpura occurs as the result of either noninflammatory or inflammatory changes in the walls of small blood vessels.

NONINFLAMMATORY PURPURA

The following types of purpura are noninflammatory: stasis purpura, due to increased intracapillary pressure; senile purpura, due to degeneration of the dermal collagen in exposed areas of the skin; scurvy, due to reduction of the intercellular material between endothelial cells; thrombocytopenic purpura, due to inadequate formation of blood platelets; and "febrile purpura with platelet thrombosis," a rare systemic fatal disease.

Histopathology. In stasis purpura, scurvy and thrombocytopenic purpura, no visible vascular changes are present and the only abnormality consists of the presence of extravasated red blood cells and, at a later stage, of hemosiderin. In senile purpura, one observes, in addition, severe degenerative changes of the dermal collagen, as seen in senile elastosis (see page 157) (Tattersall and Seville). In "febrile purpura with platelet thrombosis," one observes in the capillaries of the skin, as well as of many internal organs, degeneration and proliferation of endothelial cells and obstructing thrombi composed of platelets (Trobaugh).

INFLAMMATORY PURPURA (VASCULITIS)

The following types of purpura are caused by inflammatory changes in the walls of small blood vessels (vasculitis): bacterial purpura, due to meningococci, *Streptococcus viridans* or other microorganisms; anaphylactoid or Schoenlein-Henoch purpura which is of unknown genesis and often associated with joint pains, gastrointestinal bleeding and occasionally with glomerulonephritis; purpura due to drug allergy; and purpura associated with periarteritis nodosa.

Histopathology. There are vascular changes and an inflammatory infiltrate, in addition to the extravasation of red blood cells.

For the histologic changes in the purpuric lesions of meningococcemia and subacute bacterial endocarditis, see pages 170 and 171, respectively. For purpura associated with periarteritis nodosa, see page 311. Purpura due to drug allergy has the same histologic picture as that of anaphylactoid purpura.

ANAPHYLACTOID PURPURA. Early lesions show prominent vascular changes in the upper dermis consisting of swelling and degeneration of endothelial cells and, occasionally, of focal necrosis of the vascular wall (Gairdner; Levinson). A rather severe inflammatory infiltrate is

present predominantly, but not exclusively, around the damaged vessels (Fig. 60). It consists largely of neutrophils and varying amounts of eosinophils, with only a few lymphocytes. A characteristic feature is the presence of many scattered nuclear fragments, the result of the disintegration of neutrophils ("leukocytoclasia"). Extravasation of

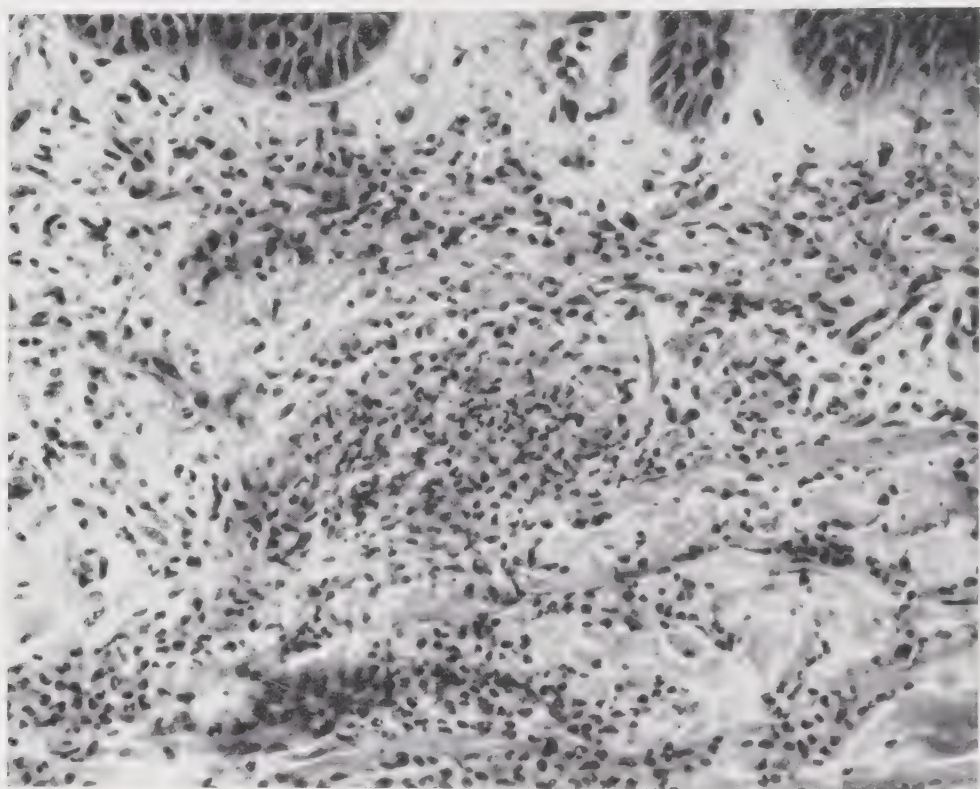


FIG. 60. Anaphylactoid purpura (inflammatory purpura). The capillaries show swelling and degeneration of endothelial cells. A rather severe inflammatory infiltrate is present, especially around the capillaries. It is composed largely of neutrophils, many of which show disintegration of their nuclei ("leukocytoclasia"). This being an early lesion, no extravasation of erythrocytes has as yet occurred. ($\times 200$)

erythrocytes is usually present, although it may be absent in the early stage of the disease.

In older lesions, extravasation of red cells usually is a prominent feature. In addition, hemosiderin may be present due to the decomposition of red cells. The endothelial lining of the vessels may show proliferation. The infiltrate contains fewer neutrophils and eosinophils and consists predominantly of lymphocytes. However, nuclear fragments are still present, as a rule.

It may be pointed out that fragmentation of the nuclei of neutrophils is prominent in the histologic picture of the Arthus phenome-

non which occurs in sensitized animals at the site of a subcutaneous injection of foreign protein. The presence of leukocytoclasia in anaphylactoid purpura would, therefore, support the view that this disease represents an allergic reaction (Ruiter and Brandsma).

PURPURA PIGMENTOSA PROGRESSIVA

(Majocchi-Schamberg)

Four diseases are included under this term: purpura annularis telangiectodes (Majocchi), progressive pigmentary dermatosis (Scham-

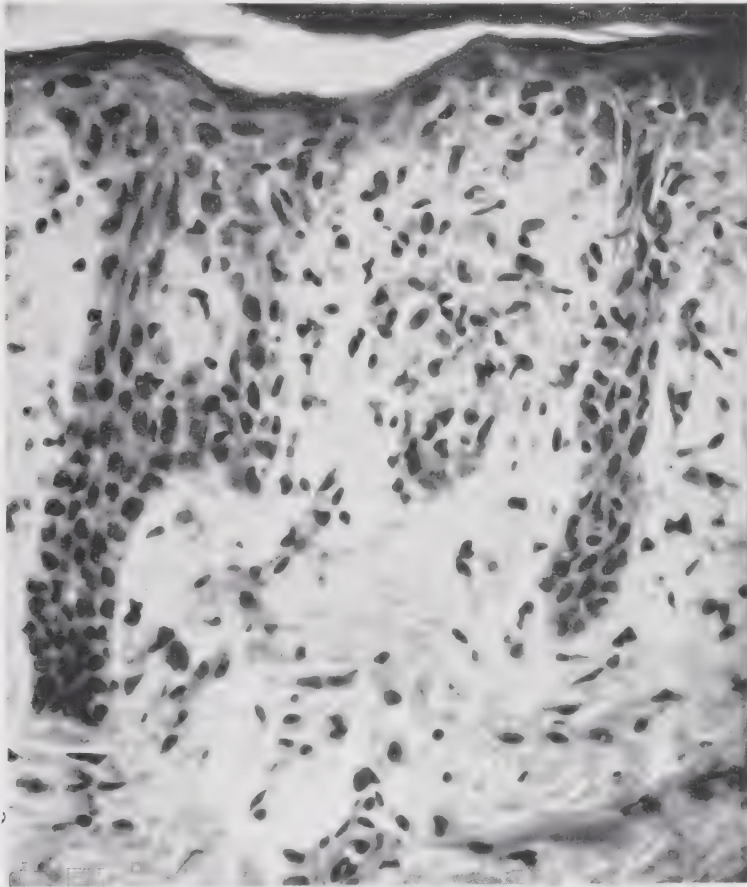


FIG. 61. Purpura pigmentosa progressiva (Majocchi-Schamberg). A group of capillaries located in a papilla show swelling, proliferation and degeneration of their endothelial cells. A small focus of extravasation of erythrocytes can be seen to the right of the group of capillaries. ($\times 400$)

berg), pigmented purpuric lichenoid dermatitis (Gougerot and Blum) and angioma serpiginosum. They are so closely related to one another that often they cannot be differentiated on clinical or histologic

grounds. Their separation into different entities, therefore, is unwarranted (Randall, Kierland and Montgomery). The term *purpura pigmentosa progressiva* is suggested for this disease.

The basic process is a chronic capillaritis of unknown cause occurring in the upper dermis and leading to capillary fragility. Clinically, the primary lesion consists of purpuric puncta appearing in groups and slowly extending so that various-sized patches form. Gradually, pigmentation, due to the deposition of hemosiderin, supervenes and, in cases of long standing, may dominate the clinical picture. Inflammatory signs (such as erythema, scaling and papules) may be present or absent. In most instances, the disease is limited to the lower extremities but may be more or less generalized. The disease, though chronic, is harmless.

Histopathology. In early lesions, the capillaries of the upper dermis show swelling, degeneration and proliferation of their endothelial cells. Often the number of capillaries appears to be increased. Small amounts of extravasated red cells are usually found in the vicinity of some capillaries. A cellular infiltrate, consisting largely of lymphocytes together with some histiocytes and occasionally a few neutrophils, is present in the upper dermis, especially in the vicinity of the capillaries. The inflammatory infiltrate may invade the lower epidermis and provoke mild liquefaction degeneration of the basal-cell layer, mild spongiosis of the stratum malpighii and patchy parakeratosis.

In older lesions, the number of capillaries is usually increased. Some show proliferation of their endothelium and others dilatation of their lumen. Extravasated red cells may no longer be present, but hemosiderin is almost always found, though in varying amounts. The inflammatory infiltrate is less pronounced than in the early stage. The epidermis may show slight atrophy with absence of the rete ridges.

Differential Diagnosis. It may be difficult to differentiate *purpura pigmentosa progressiva* histologically from stasis dermatitis because inflammation, extravasation of erythrocytes and deposits of hemosiderin occur in both. However, the process extends much deeper in stasis dermatitis and, in addition, fibrosis of the dermis and fibrous thickening of the walls of medium-sized vessels in the lower dermis is commonly present (see page 73). Anaphylactoid purpura differs from *purpura pigmentosa progressiva* by the predominance of neutrophils in the infiltrate and the presence of leukocytoclasia (see page 128).

RELAPSING FEBRILE NODULAR NONSUPPURATIVE PANNICULITIS (WEBER-CHRISTIAN DISEASE)

This disease is characterized by the appearance of crops of indurated, tender nodules and plaques in the subcutaneous fat. As the lesions involute, they often leave a depression in the skin. The overlying skin shows, as a rule, no involvement other than mild erythema. In occasional instances, the nodules liquefy, the overlying skin breaks down and an oily liquid is discharged (liquefying panniculitis).

Histopathology. Histologically, the disease can be divided into three stages. The first two stages occur while there is induration clinically. During the third stage, depression of the skin develops. The first stage is observed only rarely because it is of short duration. It is probable that it does not always occur. Most sections show a combination of the changes of the second and the third stage.

In the first stage (acute inflammatory stage), there is, between the fat cells, an inflammatory infiltrate composed of polymorphonuclear leukocytes, lymphocytes and histiocytes. Polymorphonuclear leuko-

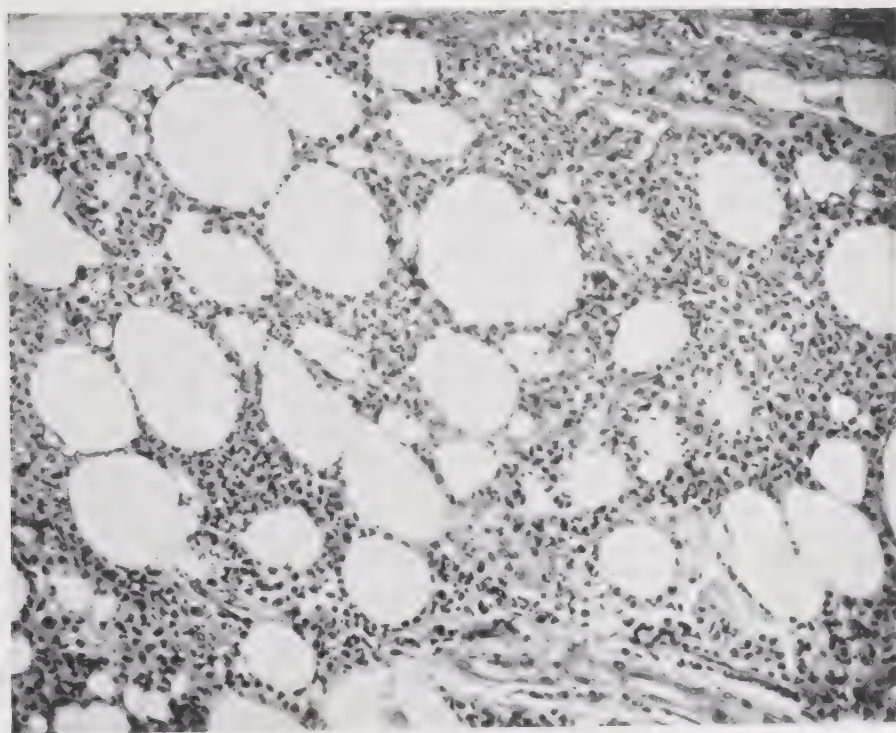


FIG. 62. Relapsing febrile nodular nonsuppurative panniculitis. First stage. An acute inflammatory infiltrate composed predominantly of polymorphonuclear leukocytes is seen between the fat cells. ($\times 200$)

cytes may predominate (Fig. 62) (Ungar; Lever). Abscess formation does not occur.

In the second stage (macrophagic stage), the infiltrate consists predominantly of histiocytes. A few lymphocytes and plasma cells are present. The histiocytes are seen invading and digesting the fat cells. Such histiocytes (macrophages) are large and have a foamy cytoplasm. Such histiocytes (macrophages) are large and have a foamy cytoplasm

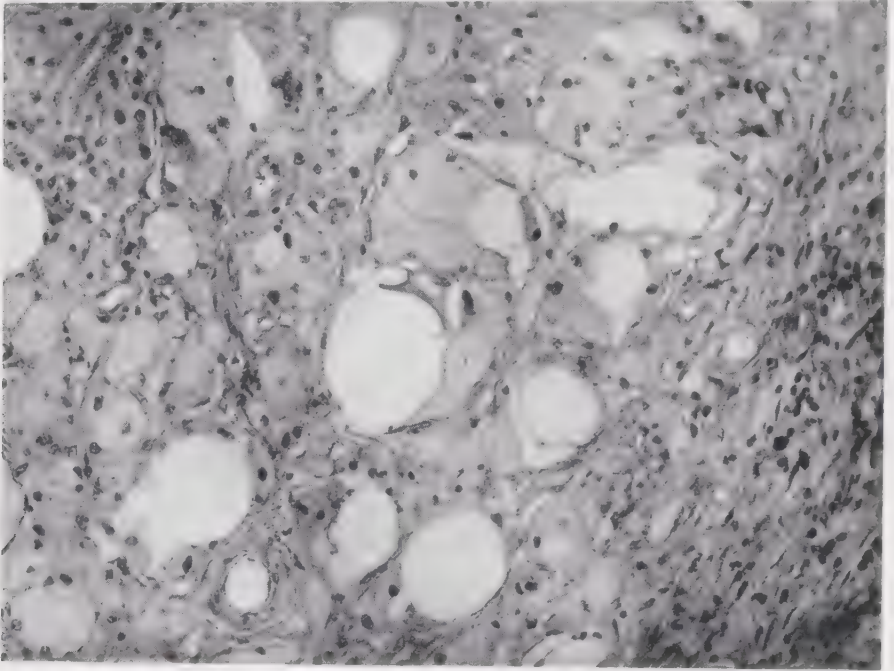


FIG. 63. Relapsing febrile nodular nonsuppurative panniculitis. Second and third stages. The left side and the center of the field show the second stage: foam cells (macrophages) invading and digesting the fat cells. The right side shows the third stage: replacement by fibrotic connective tissue. ($\times 100$)

(Fig. 63). Some of them are multinucleated. In some areas, numerous macrophages with foamy cytoplasm completely replace the fat cells.

In the third stage (fibroblastic stage), fibroblasts intermingled with lymphocytes replace the macrophages. Collagen is laid down with resulting fibrosis.

The epidermis and the dermis show no involvement. In some cases, the subcutaneous vessels show pathologic changes, such as edema and thickening of their walls (Cummins and Lever; Tilden, Gotshalk and Avakian).

In cases of liquefying panniculitis (Shaffer; Binkley), the second, macrophagic stage, instead of being followed by fibrosis, is followed

by liquefaction of the foam-cell infiltrate. One finds an amorphous foamy matrix in which the nuclei of foam cells as well as lymphocytes and some polymorphonuclear leukocytes are suspended.

It is now established that the disease may affect the internal adipose tissue. Four autopsies are on record. In three of them, internal lesions of panniculitis were present which had the same histologic appearance as the cutaneous lesions. Involvement was slight in one of these cases (Spain and Foley) but extensive in two (Ungar; Mostofi and Engleman). However, only one of these patients (Mostofi and Engleman) had died definitely as a result of this disease.

Differential Diagnosis. The histologic appearance of nodular panniculitis is diagnostic in the second stage because there is no other condition in which one finds such preponderance of foam cells in the subcutaneous fat. In foreign-body granuloma, one usually finds, besides foam cells, a great variety of other cells including foreign-body giant cells.

SCLEREMA NEONATORUM

Two types occur: generalized sclerema neonatorum and nodular sclerema neonatorum (subcutaneous fat necrosis of the newborn, adiponecrosis subcutanea neonatorum, lipophagic granuloma).

In generalized sclerema neonatorum, the skin of the entire body has a waxlike appearance and is hard, dry and cold. Death usually occurs within a week. In nodular sclerema neonatorum, one observes deep-seated indurated areas in the subcutaneous fat. The process is localized and self-limited, the lesions requiring about 4 months to disappear. The general health is not affected.

Histopathology. The fundamental lesion is the same in generalized sclerema neonatorum and in nodular sclerema neonatorum (Zeek and Madden; Flory), and both may occur simultaneously (Eichenlaub and Sandler). One finds degeneration, necrosis and crystallization of the subcutaneous fat together with an inflammatory reaction and fibrosis. It is possible that the disease is due to a delay in the maturation of the fat and that, on account of this, there is an unusually low oleic acid content of the fat so that it solidifies more easily than normally (Noojin, Pace and Davis).

GENERALIZED SCLEREMA NEONATORUM. The fat cells of the subcutis vary greatly in size and shape. In some areas they are necrotic and have lost their outline. Needle-shaped empty clefts lie singly or in radial arrangement inside of fat cells (Fig. 64). In frozen sections, these clefts are found to be occupied by crystals. The crystals fail to stain with fat stains. Some of them are doubly refractile in the polarizing microscope (Reich; Zeek and Madden). The chemical composi-

tion of the crystals is not yet established fully. Most investigators regard the crystals as those of fatty acids (McIntosh). A granulomatous infiltrate is present mainly at the periphery of the fat lobules but also in scattered foci throughout the lobules. The infiltrate is composed of lymphocytes, histiocytes, foreign-body giant cells and fibroblasts. The septa between the fat lobules are considerably thickened.

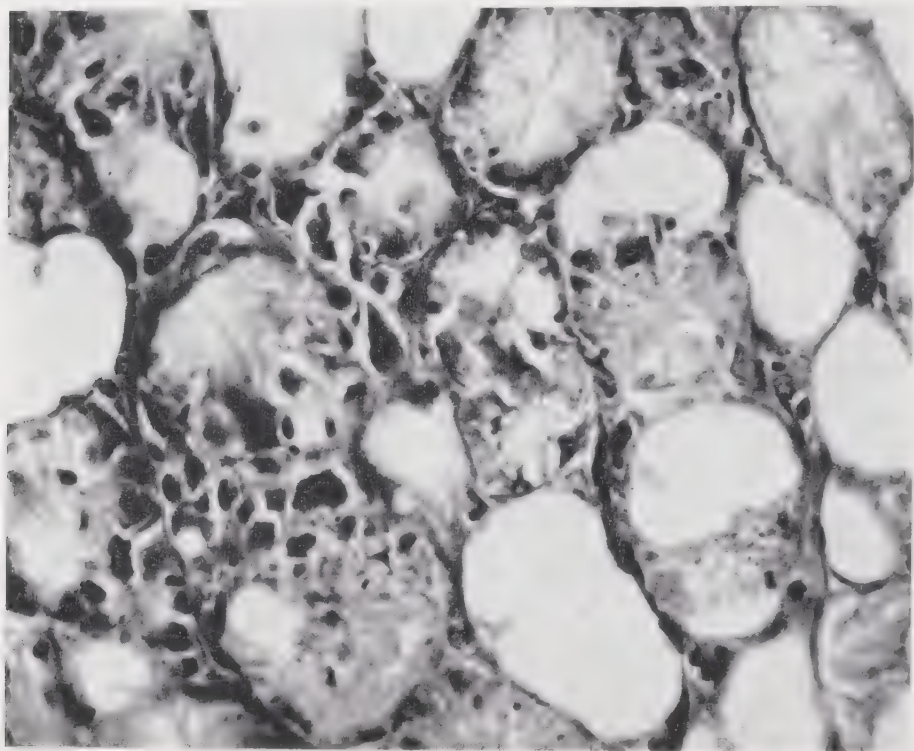


FIG. 64. *Sclerema neonatorum* (subcutaneous fat necrosis of the newborn). Several fat cells contain needle-shaped clefts in a radial arrangement. These clefts are indicative of fat crystals. The fat crystals themselves are not visible because of fixation in Helly's solution, which dissolves fat. A granulomatous infiltrate containing foreign-body giant cells is present between the fat cells. ($\times 400$)

In two cases of generalized sclerema neonatorum, autopsy revealed in the visceral fat lesions which were histologically identical with those of the subcutaneous fat. In one case (Zeek and Madden), the lesions were widely distributed. In the other case (Flory), they were limited to the perirenal fat and to the fat about the ribs.

NODULAR SCLEREMA NEONATORUM (SUBCUTANEOUS FAT NECROSIS OF THE NEWBORN). One observes, as a rule, a more marked inflammatory reaction and a much larger number of foreign-body giant cells than in generalized sclerema neonatorum (Fig. 64). The foreign

body giant cells may contain fat crystals (Fox). Healing takes place with fibrosis.

Differential Diagnosis. The histologic picture of sclerema neonatorum differs from that of relapsing febrile nodular nonsuppurative panniculitis by the presence of fat crystals and the absence of foam cells.

HEREDITARY EDEMA OF THE LEGS (MILROY'S DISEASE)

This disease occurs as a solid, white, indolent and persistent edema of the lower extremities. Usually several members of a family are affected.

Histopathology. The dermis and especially the subcutaneous fat show severe interstitial edema. There is an increase in the amount of collagen in the dermis and segmentation of the subcutaneous fat by thick strands of collagen. The capillaries and the lymphatics are dilated and increased in number and show slight perivascular lymphocytic infiltration. The walls of the larger blood vessels may be thickened by fibrosis.

CHONDRODERMATITIS NODULARIS CHRONICA HELICIS

In this disorder, one or several small, well-defined, hard, painful nodules are found on the upper margin of the ear. The surface of the nodules often is hyperkeratotic. After removal of the keratotic layer, a small ulcer may be visualized.

Histopathology. The epidermis shows hyperkeratosis, irregular acanthosis and usually also central ulceration. The dermis and, frequently, also the perichondrium are permeated by a chronic inflammatory, granulomatous infiltrate composed of lymphocytes, plasma cells, histiocytes and fibroblasts. The infiltrate may contain areas of necrosis invaded by neutrophils. It may also cause superficial erosion of the cartilage. The cartilage shows degeneration of varying extent and severity. There may be just focal disappearance of the cartilage cells, but occasionally there is focal degeneration so that the cartilage, instead of staining blue, stains homogeneously pink with hematoxylin and eosin in the affected areas.

The pathogenesis is not clear. Whereas most authors regard degenerative changes in the cartilage as the primary change (Foerster; Ebenius), Newcomer recently has pointed out that similar degenerative changes occur in the aural cartilage with advancing age. It is probable that trauma, such as frostbite or pressure, causes focal degeneration in the dermis of the ear. Due to poor vascularization

in the affected area, repair does not ensue and the lesion becomes a focus of chronic inflammation.

SCABIES

Scabies, which is caused by the itch mite *Acarus scabiei*, presents burrows as its characteristic lesion. The burrows, produced by the female mite, occur on the palmar surfaces of the hands and the fingers.

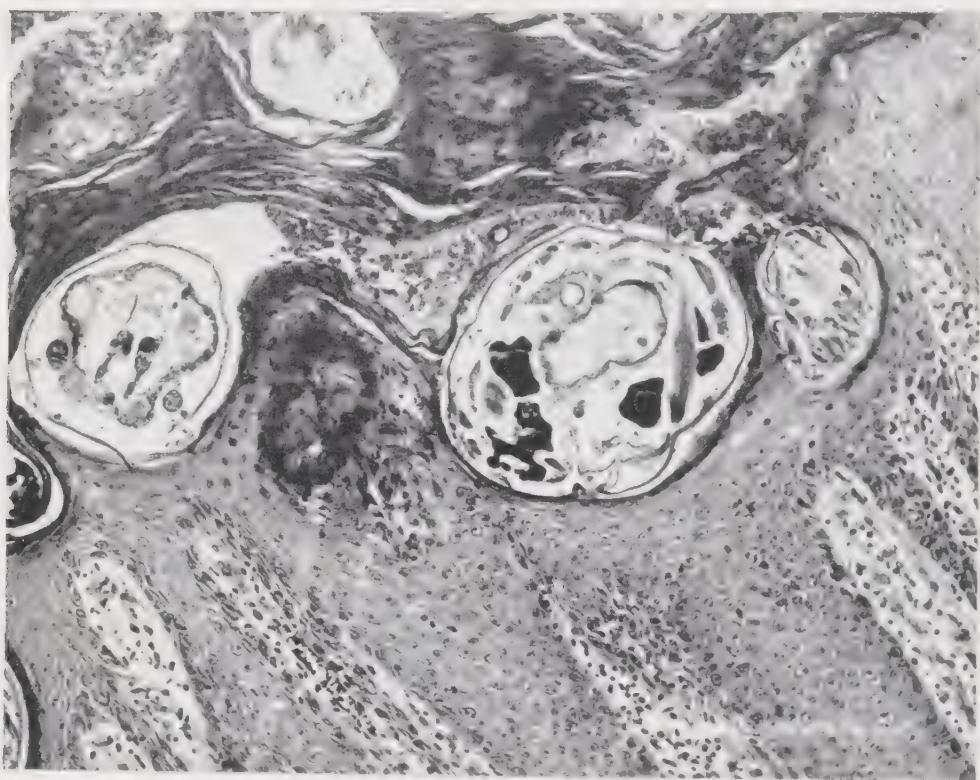


FIG. 65. Scabies (Norwegian scabies). Two female mites are located entirely within the horny layer of the epidermis. ($\times 200$) (Robert N. Buchanan, Jr., M.D.)

on the interdigital skin, on the flexor surfaces of the wrists, on the nipples of women and on the genitals of men. They appear as fine, angular or tortuous, blackish threads, a few millimeters long. Often a vesicle is visible near the blind end of the burrow. In addition to the burrows, scabies presents a papular eruption which is usually most pronounced on the abdomen, the lower portions of the buttocks and the anterior axillary folds.

In especially susceptible individuals, the clinical picture of so-called Norwegian scabies may result, showing diffuse hyperkeratosis, scaling and crusting of the skin and burrows everywhere on the skin, even on the face and the scalp.

Histopathology. Histologic examination reveals the burrow in almost the whole of its course limited to the horny layer. Only the extreme, blind end of the burrow is either in contact with or extends into the stratum malpighii. The female mite is situated at the blind end of the burrow (Fig. 65). Its head is bored more or less deeply into the stratum malpighii. Intracellular and intercellular edema is present in the stratum malpighii beneath the mouth parts of the mite to such extent that vesicle formation often results. The mite thus takes its food in fluid form. The dermis beneath the burrow shows a chronic inflammatory infiltrate which is composed predominantly of lymphocytes.

Norwegian scabies shows a much greater number of burrows than ordinary scabies so that almost every section shows several of them (Ingram).

INSECT BITES

Insect bites, especially when caused by ticks, may cause persistent lesions which pose a diagnostic problem clinically as well as histologically. The clinical appearance of the lesions usually is that of a firm papule or of a nodule with or without central ulceration.

Histopathology. The epidermis frequently shows pseudo-epitheliomatous hyperplasia (see page 334). The dermis presents a dense, granulomatous infiltrate which often extends into the subcutaneous fat. It consists principally of eosinophils and plasma cells admixed with lymphocytes and histiocytes. Some of the histiocytes occasionally show nuclei that are hyperchromatic, show mitotic figures or are binucleated. In some lesions, large lymphoid follicles with germinal centers are observed (Winer and Strakosch; Allen). In rare instances, parts of the insect are found in the dermis either free in the tissue surrounded by a foreign-body reaction or within an epidermal inclusion cyst (Allen).

Differential Diagnosis. If parts of the insect are present in the section, the diagnosis is obvious. In their absence, the true nature of the lesion may be missed easily. The pseudo-epitheliomatous hyperplasia must be differentiated from squamous-cell carcinoma (see page 329). The presence of mitotic figures in the histiocytes together with the large number of eosinophils may suggest mycosis fungoides; the presence of lymphoid follicles may suggest lymphocytoma cutis; and the binucleated histiocytes, if present, require differentiation from the Sternberg-Reed cells of Hodgkin's disease. However, the abundance of plasma cells in association with the eosinophils usually rules out lymphoma.

LICHEN URTICATUS (PAPULAR URTICARIA)

This is a recurrent, pruritic eruption occurring, especially in children, during the summer months. The lesions consist of edematous

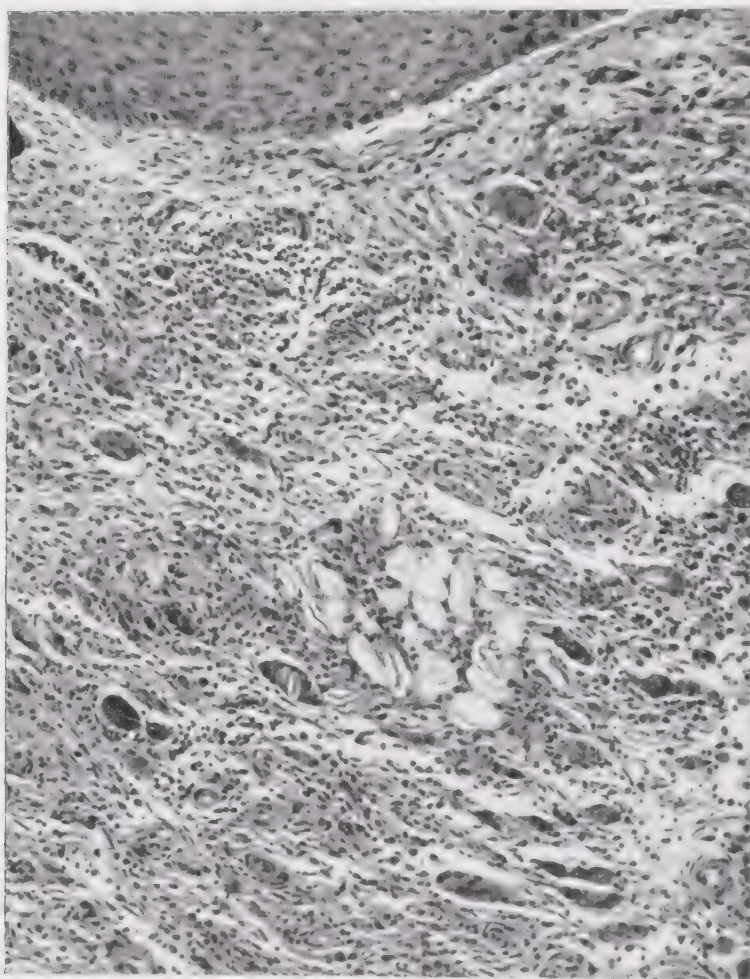


FIG. 66. Foreign-body granuloma caused by a silk suture. The silk suture is located in the center of the field. Around it there is a severe inflammatory infiltrate containing numerous foreign-body giant cells. ($\times 200$)

papules. Sensitivity to flea and bedbug bites is now generally regarded as the usual cause (Goldman; Shaffer, Spencer and Blank).

Histopathology. The appearance is nonspecific. Acanthosis and, in some cases, hyperkeratosis are present. The stratum malpighii shows intercellular as well as intracellular edema. A rather pronounced chronic inflammatory infiltrate is present around the vessels of the upper dermis.

FOREIGN-BODY GRANULOMAS

Many foreign substances when injected, or accidentally implanted, into the skin may cause a foreign-body reaction. In addition, certain

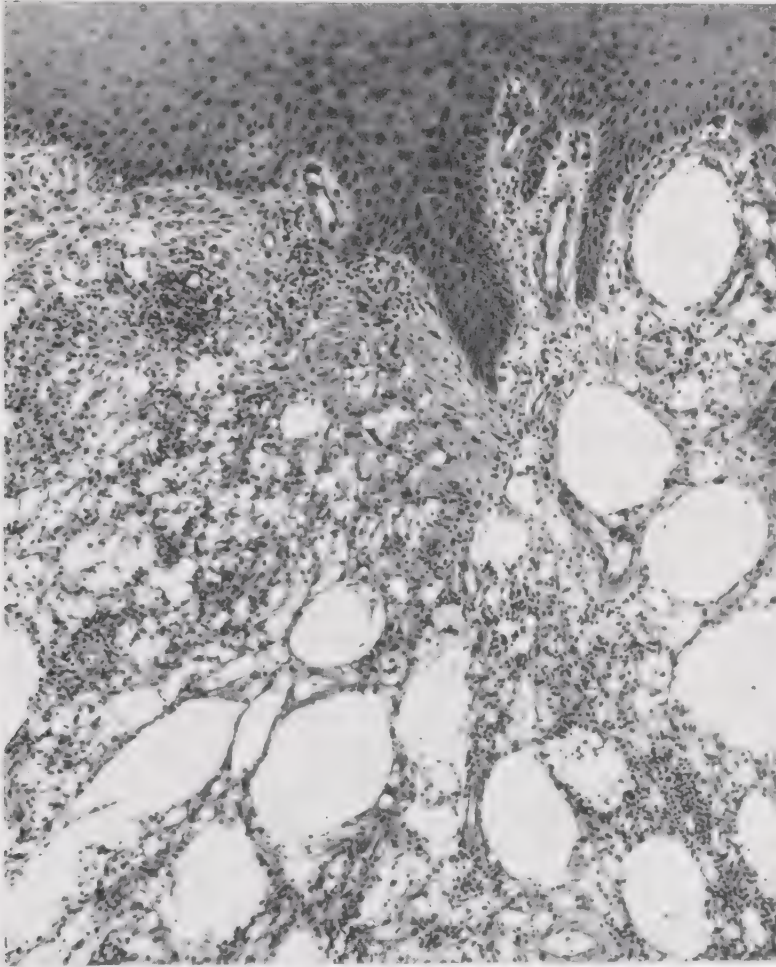


FIG. 67. Lipid granuloma caused by mineral oil (paraffinoma). The many large and small ovoid or round cavities which give the section a "Swiss cheese" appearance represent spaces filled with mineral oil (paraffin). ($\times 200$)

substances formed within the body may produce a foreign-body reaction when deposited in the dermis or in the subcutaneous tissue. Examples are the foreign-body reactions occurring in gout, calcifying epithelioma of Malherbe and ruptured epidermal and sebaceous cysts.

Histopathology. A typical foreign-body reaction shows, around the foreign material, histiocytes and foreign-body giant cells (for

their description, see page 36). In addition, lymphocytes and plasma cells are present (Fig. 66). The histiocytes and the giant cells often exhibit phagocytic activity and then contain some of the foreign material.

Some foreign-body granulomas have a rather specific appearance. Among them are lipid, tattoo, silicon and beryllium granulomas.

LIPID GRANULOMA (PARAFFINOMA)

Granulomas following injections of oily substances such as mineral oil (paraffin), cotton oil, or camphor oil occur as irregular, hard, nodular subcutaneous swellings. Ulceration may develop.

Histopathology. Histologically, lipid granulomas have a "Swiss cheese" appearance because of the presence of numerous ovoid or round cavities (Fig. 67). These cavities represent spaces occupied by the oily substance (Conrad and Weiss). The spaces between the cavities are taken up by an infiltrate composed largely of lymphocytes and some plasma cells. In addition, there are groups of histiocytes some of which, due to the ingestion of lipid, have a foamy cytoplasm. Variable numbers of foreign-body giant cells are present. In older lesions, fibrosis is prominent.

Under the term sclerosing lipogranuloma, Smetana and Bernhard have reported as a post-traumatic process subcutaneous granulomas with the same histologic picture as just described. However, Best, Mason, DeWeerd and Dahlin have thrown serious doubt on the existence of such an entity. Investigating two similar cases, they found by chemical analysis that the "lipid" material was not body fat but mineral oil. The "lipid" material in their cases stained with Sudan 4 but not with osmic acid.

TATTOO GRANULOMA

Histopathology. Ordinary tattoos show diffusely scattered granules in the upper half of the dermis within phagocytes and lying free in the tissue, without any inflammatory reaction.

However, if an inflammatory reaction occurs, due to allergy, the inflammatory infiltrate shows, aside from the phagocytes, numerous lymphocytes with an admixture of many eosinophils and a few plasma cells (Rostenberg, Brown and Caro).

SILICON GRANULOMA

Silicon may be introduced into the skin through the contamination of lacerations with particles of soil. Such wounds heal at first and then, many months or years later, indurated nodules develop in the skin or the subcutaneous tissue.

Histopathology. The histologic picture is indistinguishable from that of sarcoidosis (see page 188) except for the presence in some of the giant cells of colorless, spiculated, crystalline particles varying in size from barely visible to 100 microns in length. When examined with the polarizing microscope, these particles are seen to be doubly refractile (Ayers, Ober and Hamilton; Sommerville and Milne).

BERYLLIUM GRANULOMA

Beryllium granulomas of the skin may form in two different ways (Grier, Nash and Freiman). They may arise as a manifestation of

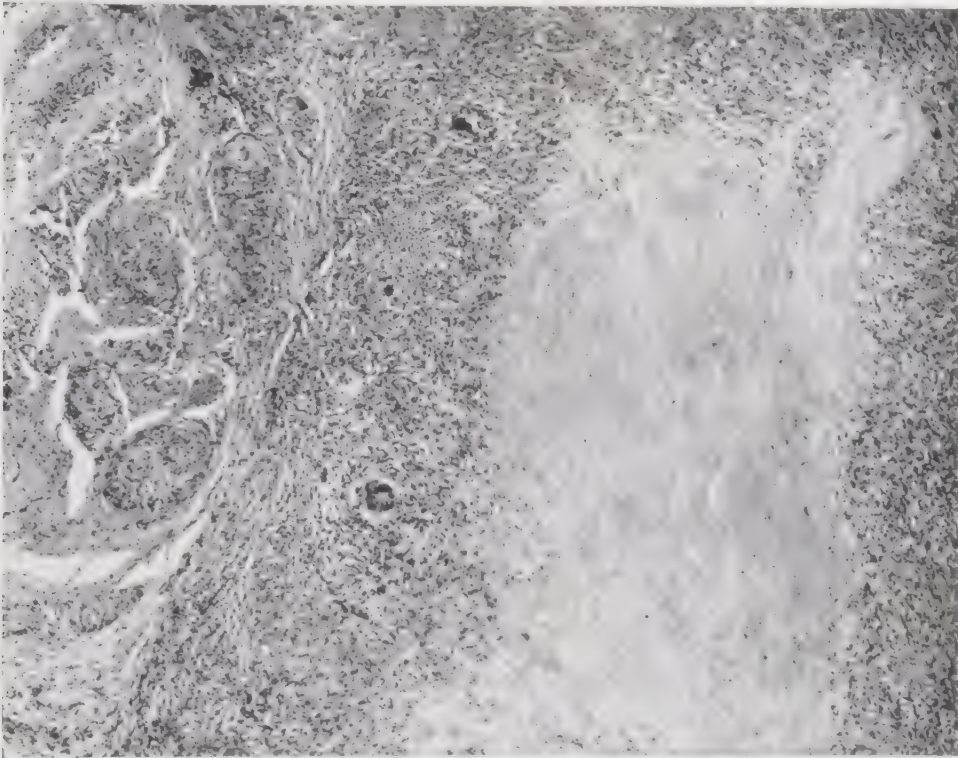


FIG. 68. Beryllium granuloma caused by laceration with a fluorescent light tube. There is a large area of caseation necrosis surrounded by tuberculoid granulation tissue. To the left, several sarcoid-like epithelioid-cell islands are present. ($\times 100$)

systemic berylliosis, in which case it must be assumed that particles of beryllium reached the skin through the circulation; or they may develop following a laceration of the skin through which beryllium entered the tissue. Such lacerations were observed some years ago from cuts with fluorescent light bulbs which then were coated with a mixture containing beryllium oxide.

The cutaneous granulomas of systemic berylliosis consist of small

nodules over which the skin remains intact. They are always few in number. The most serious lesion in systemic berylliosis is the chronic progressive pneumonitis which is frequently fatal.

The cutaneous granulomas following laceration show as first sign incomplete healing of the laceration, followed by swelling, induration and tenderness and, finally, central ulceration.

Histopathology. The cutaneous granulomas of systemic berylliosis often are indistinguishable from sarcoidosis (Hardy and Tabershaw). Occasionally, however, a moderate amount of caseation necrosis is present in some of the epithelioid-cell islands. The quantity of beryllium present in the lesions is too small to be demonstrable by spectrographic analysis.

The cutaneous granulomas following laceration show, as a rule, more caseation necrosis than the granulomas of systemic berylliosis. The caseation necrosis not only may be present within some of the epithelioid-cell islands but also may affect the entire center of the lesion (Fig. 68) (Neave, Frank and Tolmach). A collar of lymphocytes often surrounds some of the epithelioid-cell islands, giving them the appearance of true tubercles. Occasionally, Schaumann bodies, just like those of sarcoidosis, are present (Grier, Nash and Freiman). The epidermis shows acanthosis and may show ulceration. In some cases, the presence of beryllium has been demonstrated by spectrographic analysis (Dutra).

SWIMMING-POOL GRANULOMA

Abrasions in swimming pools may lead to circumscribed areas of nodular infiltration on the face resembling lupus vulgaris (Hellerström) or to granulomatous, verrucous lesions on the knee or elsewhere resembling tuberculosis verrucosa cutis (Rees and Bennett). The lesions usually heal within 3 to 9 months.

Histopathology. The histologic picture is similar to that of lupus vulgaris (Hellerström) or of tuberculosis verrucosa cutis (Rees and Bennett). Hellerström regarded his cases as instances of inoculation lupus vulgaris, but inoculations of tissue into guinea pigs have given negative results in all reported cases and Hellerström found acid-fast bacilli in the tissue in but one of his six cases. Thus a tuberculous cause is not established. Silicon granuloma is also unlikely because no crystalline particles were ever observed. The cause remains obscure.

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9

Eruptions Due to Drugs

Allergic reactions to drugs may cause various eruptions identical in their clinical appearances to cutaneous diseases occurring also as idiopathic entities. Drugs may cause, for instance, urticaria, erythema multiforme, erythema nodosum, dermatitis, including generalized exfoliative dermatitis, purpura, folliculitis and periarteritis nodosa. The histologic picture is the same in these diseases whether they are due to a drug or occur in their idiopathic form.

Only histologic changes more or less specific for eruptions due to drugs will be discussed.

FIXED DRUG ERUPTION

Fixed drug eruptions are circumscribed lesions which persistently recur at the same site at each administration of the allergenic drug. The most common type of fixed drug eruption consists of one or several slightly elevated, erythematous plaques which on healing leave pigmented areas. Fixed drug eruptions may occur after the ingestion of phenolphthalein and coal-tar derivatives such as aminopyrine and acetophenetidin.

Histopathology. There is an increase in melanin in the basal cells and in the dendritic cells of the epidermis. Melanin is present in the upper dermis. It is found predominantly in histiocytes (melanophores) but also free in the tissue. The superficial capillaries are surrounded by a mild inflammatory infiltrate composed of lymphocytes and histiocytes (Weiss and Kile; Chaïgin and Leifer).

QUINACRINE HYDROCHLORIDE (ATABRINE) DERMATITIS

Quinacrine hydrochloride (Atabrine) may cause a subacute or a chronic dermatitis, lichen-planus-like lesions and exfoliative dermatitis (Bereston). In some patients, the eruption is followed by anhidrosis in the involved areas.

Histopathology. The histologic picture is usually that of a non-specific chronic dermatitis. In lesions that clinically resemble lichen planus, the histopathologic picture often resembles that of lichen

planus too. As a rule, however, the bandlike infiltrate is not so dense as in lichen planus and may contain eosinophils which are not present in true lichen planus (Wilson). In many cases, one observes hyperkeratosis with keratotic plugging of pilosebaceous follicles. Numerous melanophores may be present in the dermis (Alden and Frank).

In patients in whom anhidrosis develops in areas of quinacrine hydrochloride dermatitis, one may observe atrophy of the dermal portions of sweat ducts and dilatation and atrophy of the sweat glands. Focal inflammation may be present about the sweat glands (Sulzberger, Herrmann and Zak).

EXFOLIATIVE DERMATITIS DUE TO DRUGS

The most common drugs to cause exfoliative dermatitis are arsphenamine, gold salts, the sulfonamides and phenobarbital.

Histopathology. The exfoliative dermatitis caused by these drugs has the same histologic appearance as exfoliative dermatitis due to other causes (see page 74 and Fig. 27).

Changes in the internal organs may be present, such as interstitial myocarditis (Brown and McNamara; French and Weller; Winer and Baer), interstitial nephritis (Winer and Baer) and fatty degeneration of the liver with inflammatory infiltration about the portal canals (Winer and Baer).

BROMODERMA

Prolonged ingestion of bromides may cause the formation of granulomatous, verrucous plaques, which are called bromoderma. They occur usually on the lower extremities.

Histopathology. There are papillomatosis and considerable downward proliferation of the epidermis, often of such degree as to produce the picture of pseudo-epitheliomatous hyperplasia. Islands of epidermis may be found deep in the dermis. Intra-epidermal abscesses frequently are present in the surface epidermis as well as in the downward proliferations of the epidermis (Bloch and Tenchio) (Fig. 69). The dermis shows an extensive granulomatous infiltrate which may reach down into the subcutaneous layer. It is composed of a great variety of cells including lymphocytes, plasma cells and histiocytes. Neutrophils are usually numerous, and abscesses may be found scattered through the infiltrate. Eosinophils are few or absent. The blood vessels are increased in number, are dilated and show proliferation of their endothelium. Small areas of hemorrhage are often seen within the infiltrate.

Differential Diagnosis. The histologic picture of bromoderma is suggestive but not diagnostic. Pyoderma gangrenosum may show, at

the margin of an ulcer, an identical histologic picture, including intra-epidermal abscesses. Intra-epidermal abscesses are also observed in older lesions of pemphigus vegetans and in blastomycosis. Pemphigus vegetans differs from bromoderma by the large percentage of eosinophils in the intra-epidermal abscesses and in the granuloma-

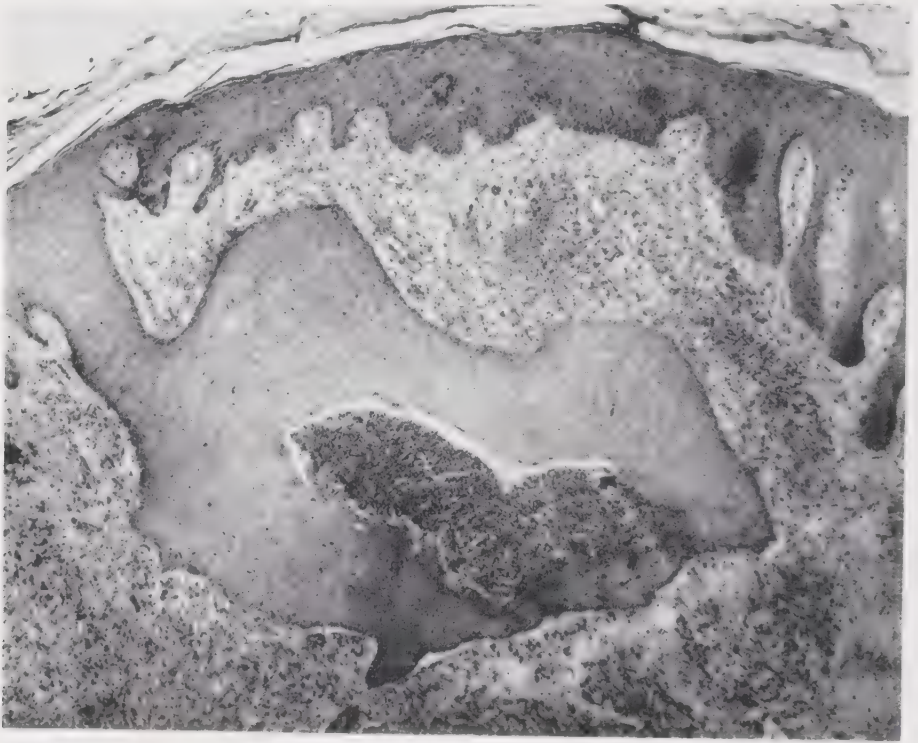


FIG. 69. **Bromoderma.** There is downward proliferation of the epidermis. A large intra-epidermal abscess is shown. The dermis contains a granulomatous infiltrate. ($\times 50$)

tous infiltrate (see page 80). Blastomycosis is easily differentiated by its numerous giant cells and the presence of yeast cells in them.

IODODERMA

Iododerma is characterized by granulomatous lesions which may have the same clinical appearance as bromoderma. As a rule, however, there is less verrucous proliferation and greater tendency to ulceration.

Histopathology. Histologically, iododerma differs from bromoderma by showing less epithelial proliferation. The granulomatous infiltrate frequently destroys the epidermis, resulting in ulceration. The infiltrate may be composed predominantly of histiocytes, some of which may show mitotic figures and hyperchromatic nuclei, so that

distinction from lesions of mycosis fungoides in the tumor stage may be almost impossible (Eller and Fox; Hollander and Fetterman).

ARGYRIA

This condition, caused by prolonged ingestion of silver salts or their local application to the mucous membranes, is characterized by



FIG. 70. Argyria. Silver granules are present in the membrana propria of the sweat glands. In some places, the granules are so dense that they form a solid black band. ($\times 400$)

bluish gray, slate-colored discoloration of the entire skin, most pronounced on the exposed portions of the skin.

Histopathology. Silver is found in the dermis, predominantly extracellularly, as fine, small, round, brownish particles of uniform size. It is never seen in the epidermis or its appendages. The silver particles measure less than 1 micron in diameter and lie singly as well as in clumps. Although visible in routine stains, they appear more clearly in sections stained lightly with polychrome methylene blue. However, the best method for the demonstration of silver granules is by dark-field illumination. If sections are placed under a dark-field microscope, the silver appears as brilliantly refractile, white granules

against a dark background. Many more granules can be seen than with direct illumination.

The silver granules are most numerous in the *membranae propriae* surrounding the sweat glands (Fig. 70) and in the subepidermal dermis. In addition, silver particles may be seen in the connective-tissue sheaths about the hair follicles and the sebaceous glands, in the walls of blood vessels, particularly their intima and adventitia, in the *arrectores pilorum* and the nerves, and diffusely scattered through the middle and the lower dermis. Elastic-tissue stains reveals a predilection of the granules of silver for elastic fibers. The location of silver in elastic fibers explains the presence of fingerlike chains of granules projecting into the papillary bodies (Hill and Montgomery). In many cases, one finds increased amounts of melanin in the basal layer of the epidermis and melanin-laden chromatophores in the dermis.

Silver is deposited not only in the skin but also in internal organs. It is found particularly in the intima of blood vessels and in the connective tissue of the internal organs. Analogous to the marked involvement of the basement membrane of the sweat glands, the basement membranes around the acini of the testes and of the choroid plexus are particularly rich in granules (Harker and Hunter).

Differential Diagnosis. Histologic differentiation of argyria from other kinds of pigmentation is made readily. Melanin and hemosiderin possess larger granules, which lie to a great extent intracellularly in chromatophores and are nonrefractile with dark-field illumination. In pigmentation due to mercury, whether from the use of creams or in tattoo marks, the mercury is deposited in large, coarse granules throughout the epidermis and the dermis without any special affinity for the *membrana propria* of the sweat glands. For differentiation from chrysiasis, see below.

CHRYSIASIS

In chrysiasis, which may follow the parenteral use of gold salts, the skin of the exposed parts shows an ash-gray discoloration.

Histopathology. Gold granules are light-refractile with dark-field examination like silver granules, but they are larger and more irregular in size than silver granules. In contrast to silver granules, they are found predominantly within cells. They lie in the endothelial and the perithelial cells of capillaries and in macrophages throughout the upper dermis. Only occasionally do granules lie free in the tissue spaces (Schmidt). In some instances, gold particles are found in the basal cells of the epidermis (Kochs).

ARSENICAL KERATOSIS AND CARCINOMA

Prolonged ingestion of inorganic arsenic frequently produces multiple arsenical keratoses which may progress into squamous-cell carcinoma. Recently, it has been suggested that not only multiple cutaneous cancers but also multiple internal cancers may be caused (Sommers and McManus). Occasionally, multiple superficial basal-cell epitheliomas form in addition to arsenical keratoses (Anderson; Montgomery and Waisman).

Arsenical keratoses resemble senile keratoses in their clinical appearance. They may occur anywhere on the skin but are found most frequently on the palms and the soles, in contrast with senile keratoses which predominate on the face and on the dorsa of the hands.

Histopathology. In early arsenical keratoses, one observes hyperkeratosis associated with acanthosis and irregular downward proliferation of the rete ridges. There usually is some degree of disorder of the squamous cells and pyknosis of some of the nuclei. The histologic picture thus resembles that of senile keratosis (see page 327).

In more advanced lesions, in addition to the above-mentioned features, the epidermis shows marked vacuolization of cells, numerous mitotic figures, clumping of nuclei within giant cells and individual cell dyskeratosis. Thus, the appearance is like that of Bowen's disease (see page 336). Frequently, vacuolization of epidermal cells is much more pronounced than in Bowen's disease. Although vacuolization of cells occurs also in Bowen's disease, this feature is not so prominent as in arsenical keratosis. The presence of numerous vacuolated cells may be regarded as diagnostic of arsenical keratosis (Montgomery and Waisman). The vacuolated cells are twice or three times as large as normal squamous cells and possess small, irregular, deeply staining nuclei. They resemble the Paget cells of Paget's disease of the nipple, except that intercellular prickles are usually present.

Ultimately, through invasion of the dermis, frank squamous-cell carcinoma may develop (see page 329). Even in the invading type of carcinoma, vacuolization, clumping and dyskeratosis remain prominent.

In lesions of arsenical keratosis and arsenical carcinoma, the presence of arsenic usually can be demonstrated by histochemical methods (Montgomery and Waisman).

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10

Degenerative Diseases

SENILE DEGENERATION

Senile changes in skin not regularly exposed to light manifest themselves clinically in thinning of the skin and atrophy of the subcutaneous fat. In exposed skin, the changes usually are much more pronounced than in skin that is not exposed and include marked wrinkling and furrowing in addition to thinning. *Cutis rhomboidalis nuchae* is a term applied to the furrowed and leathery skin occurring in old persons, especially on the back of the neck. In severely aged skin, after minor trauma, ecchymoses may occur (senile purpura).

Histopathology. In skin not regularly exposed to light, senile changes are slight. One finds flattening of the rete ridges and atrophy of the collagenous fibers; but degenerative changes in the collagen or in the elastic tissue are absent. Mild obliterative changes may be found in some of the vessels (Hill and Montgomery).

In skin exposed to sunlight, two types of degenerative changes are seen which, however, represent one and the same process: basophilic degeneration of the collagen and senile elastosis. These changes, limited to the upper third of the dermis, may start as early as in the third decade of life and progress with age.

In basophilic degeneration, the collagenous fibers appear broken up into amorphous clumps and granules which stain faintly basophilic with hematoxylin and eosin (see Plate 2).

Senile elastosis is found in areas of basophilic degeneration of the collagen when sections are stained with orcein as for elastic tissue. One then observes in the upper dermis, separated from a somewhat atrophic epidermis by a narrow band of normal collagen, masses of twisted, thick, black-staining fibers (Fig. 71). Because these fibers give the same staining reactions as elastic tissue, Unna referred to them as collastin, thinking they were the result of a merging of collagen with elastic fibers. However, recent studies by x-ray diffraction and electron microscopy suggest that the essential change in senile elastosis is degeneration of collagen fibers. Furthermore, the degenerated material can be removed—in contrast with elastic fibers—by treatment of the sections with trypsin, and at the same time the

elastic-staining properties of the skin disappear (Tattersall and Seville). This suggests that the increase in orcein-staining material is caused not by an increase in the amount of elastic tissue but by a false staining reaction of degenerated collagen. Staining of frozen sections with fat stains occasionally reveals numerous fine lipid droplets in the areas of basophilic degeneration or senile elastosis (Weidman; Percival, Hannay and Duthie).

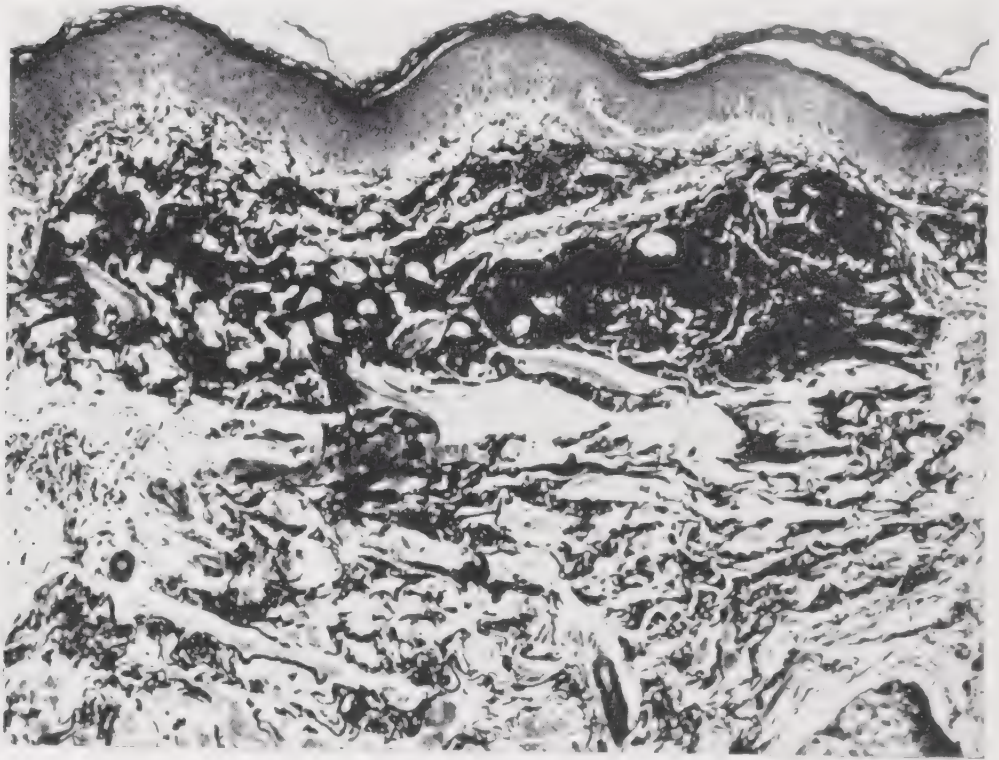


FIG. 71. Senile degeneration (senile elastosis). In the upper dermis, separated from the epidermis by a narrow band of normal collagen, there are masses of twisted, thick, degenerated collagen fibers staining black with orcein just like elastic tissue. ($\times 100$)

Differential Diagnosis. For differentiation from pseudoxanthoma elasticum, see page 56.

LICHEN SCLEROSUS ET ATROPHICUS

This disorder is characterized by flat-topped, white papules which coalesce to form white patches without any infiltration. The surface of the lesions often shows comedo-like plugs. Occasionally, the patches become bullous due to accumulation of fluid beneath the epidermis.

Lichen sclerosus et atrophicus occurs not only on the skin but also on the vulva and the glans penis. Kraurosis vulvae and balanitis

xerotica obliterans, formerly regarded as independent diseases, probably are identical with lichen sclerosus et atrophicus (see below).

Histopathology. In lichen sclerosus et atrophicus, one observes (1) hyperkeratosis with keratotic plugging, (2) atrophy of the stratum



FIG. 72. Lichen sclerosus et atrophicus. There are hyperkeratosis with follicular plugging, atrophy of the stratum malpighii, marked lymphedema of the upper dermis and an inflammatory infiltrate in the mid-dermis. The edema in the subepidermal dermis is so marked that a bulla has resulted. ($\times 100$)

malpighii with hydropic degeneration of basal cells, (3) pronounced edema and homogenization of the collagen in the upper dermis and (4) an inflammatory infiltrate in the mid-dermis (Fig. 72).

The hyperkeratosis is so marked that often the horny layer is thicker than the atrophic stratum malpighii. The stratum malpighii is reduced to a few layers of flattened cells. The cells of the basal layer show hydropic degeneration. The rete ridges often are completely



FIG. 73. **Kraurosis vulvae (lichen sclerosus et atrophicus).** There are hyperkeratosis, atrophy of the stratum malpighii and marked lymphedema of the upper dermis with homogenization of the collagen. ($\times 100$)

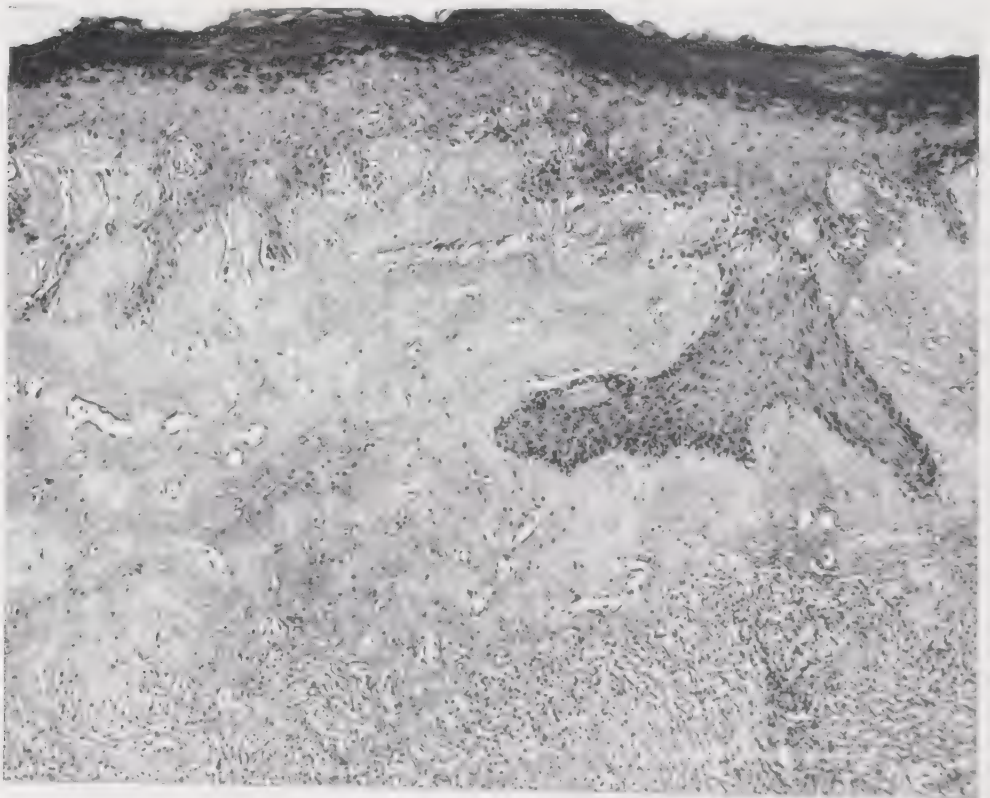


FIG. 74. See facing page for legend.

wiped out, but they may persist in some areas and even show some irregular downward proliferation. In such proliferations, hydropic degeneration of the basal cells usually is pronounced.

Beneath the epidermis there is a broad zone of pronounced edema. Within this zone, the collagenous fibers are swollen and homogeneous and contain only a few nuclei. They stain poorly with eosin and other connective-tissue stains. This change does not represent sclerosis (as the name of the disease would imply) but lymphedema. The hydropic degeneration of the basal cells together with the edema of the subepidermal collagen may lead to the formation of subepidermal bullae (Gottschalk and Cooper). These bullae may thus be classified as being due to degeneration of the basal cells (see "Classification of Bullae," page 66). The elastic fibers are sparse or even absent in the zone of edema (Nomland).

In the mid-dermis, beneath the area of edema, there is an infiltrate which usually is perivascular but at times assumes a bandlike formation. It is composed almost exclusively of lymphocytes. In lesions of long duration, the infiltrate may have almost disappeared.

KRAUROSIS VULVAE

A satisfactory classification of the atrophic lesions of the vulva has not yet evolved and, to a certain degree, the vagueness of the term *kraurosis vulvae* is responsible for this. Although some authors still regard it as an entity (Wallace and Whimster), others regard it as synonymous with lichen sclerosus et atrophicus (Laymon).

The simplest classification of the atrophic lesions of the vulva that can be offered at present is:

1. **SENILE OR PRESENILE ATROPHY.** There is atrophy of the vulvar mucosa but no stenosis of the vaginal orifice. There may be itching and, due to scratching, a vulvitis may result.

2. **LICHEN SCLEROSUS ET ATROPHICUS ("KRAUROSIS VULVAE").** Considerable atrophy with stenosis of the vaginal orifice is present. The lesions are whitish in color, sharply demarcated and may extend to the inguinal folds and the peri-anal region. Itching may be present. Because the lesions have a whitish color, on casual inspection they resemble leukoplakia; but they lack the induration observed in leukoplakia. There has been uncertainty as to whether lichen sclerosus et

FIG. 74. *Kraurosis vulvae (lichen sclerosus et atrophicus)*. There are edema of the upper dermis and a bandlike inflammatory infiltrate beneath it. In addition, there is irregular downward proliferation of the rete ridges with hydropic degeneration of the basal cells. The latter feature is typical of lichen sclerosus et atrophicus and rules out leukoplakia. ($\times 100$)

atrophicus, a perfectly harmless lesion elsewhere, may progress into leukoplakia and squamous-cell carcinoma when occurring on the vulva. Such instances recently have been reported (Wallace and Whimster), but it seems to be rare. Nevertheless, as Wallace and Whimster state, any state of atrophy occurring on the vulva has malignant potentialities.

3. LEUKOPLAKIA. One or several whitish indurated plaques are present. Leukoplakia may occur independently or secondary to senile atrophy of the vulva. Since leukoplakia is an early malignant lesion ("squamous-cell carcinoma, grade $\frac{1}{2}$," see page 328), development of squamous-cell carcinoma is common.

Histopathology. The histologic picture of senile or presenile atrophy is nonspecific, consisting of atrophy of the epidermis and a mild to moderately severe chronic inflammatory infiltrate in the upper dermis.

Lichen sclerosus et atrophicus of the vulva (*kraurosis vulvae*) shows the same histologic picture as on the skin with the exception that lesions located on the mucous membranes show no keratotic plugs (Fig. 73). Irregular downward proliferation of the rete ridges in which the basal cells show considerable hydropic degeneration occur more often than on the skin (Fig. 74). They should not be confused with the early atypical proliferations of leukoplakia which do not contain such hydropic basal cells.

Leukoplakia shows atypicality of the epidermis with irregular downward proliferation of atypical cells (see page 328). The hydropic degeneration of the basal cells seen in lichen sclerosus et atrophicus is absent.

BALANITIS XEROTICA OBLITERANS

Balanitis xerotica obliterans represents lichen sclerosus et atrophicus of the glans and prepuce (Laymon). It is a chronic, progressive, atrophic process which frequently eventuates in urethral stenosis. In very rare instances, carcinoma may supervene (Grütz).

Histopathology. The histologic picture is that of lichen sclerosus et atrophicus. Because of the absence of follicles in the areas of involvement, no keratotic plugging occurs.

STRIAE DISTENSAE

Striae distensae occur in pregnancy and obesity, and particularly in Cushing's disease. They represent linear areas of cutaneous atrophy.

Histopathology. In the early lesions, the elastic fibers are transformed into numerous faintly staining fibrillae due to fraying of the elastic fibers. In addition, there are a mild perivascular infiltrate and

a distortion of the collagen bundles. Old lesions show almost complete absence of elastic fibers in the center. At the margin, coiled and clumped elastic fibers are interspersed with fine, poorly staining fibrillae.

On the basis of these findings, Ebert has concluded that striae distensae are not due to mechanical tearing of elastic fibers alone but that degeneration of the elastic fibers precedes their disappearance in the center of the striae.

MACULAR ATROPHY (ANETODERMA)

Macular atrophy of Schweninger and Buzzi, or anetoderma, is characterized by atrophic oval patches located particularly on the trunk. The skin of the patches is thin and bluish white and bulges slightly. The lesions may give to the palpating finger the same sensation as does a hernial orifice. Early lesions may show mild erythema.

In the literature, a difference has been made between a primary idiopathic type of macular atrophy and a secondary type developing in patients with diseases such as syphilis, lupus erythematosus and acrodermatitis chronica atrophicans but in sites not clinically affected by these diseases (Scull and Nomland). It is likely that such association is merely coincidence.

Histopathology. In the early stage, the dermis may contain a mild perivascular chronic inflammatory infiltrate. The essential pathologic lesion is fragmentation and, finally, disappearance of the elastic tissue throughout the dermis. The collagen remains unaffected. Thus a diagnosis of this disease can be made only from sections stained for elastic tissue.

ATROPHODERMA RETICULATUM (FOLLICULITIS ULERYTHEMATOSA RETICULATA)

The eruption, which is limited to the sides of the face, consists of numerous, small, closely set areas of atrophy separated by narrow ridges of normal skin resulting in a reticulated appearance.

Histopathology. The epidermis shows diminution of the number of rete ridges and follicular plugging. Horn cysts caused by keratinization of hair follicles are present in the dermis. Sebaceous glands are few in number and small in size. In addition, one observes degeneration of the collagen and fragmentation of the elastic fibers.

COLLOID MILIUM (COLLOID DEGENERATION OF THE SKIN)

Colloid milium is characterized by pinhead-sized, round, sharply circumscribed, yellowish nodules of the skin. The nodules have a

translucent appearance and, on puncture, give exit to a soft, gelatinous mass. The forehead is the site of predilection.

In occasional instances, instead of small nodules, large plaquelike lesions are present. To such cases, the term colloid degeneration of the skin has been applied (Reuter and Becker).

Histopathology. Histologically, colloid milium is characterized by the presence of circumscribed masses of colloid material in the sub-

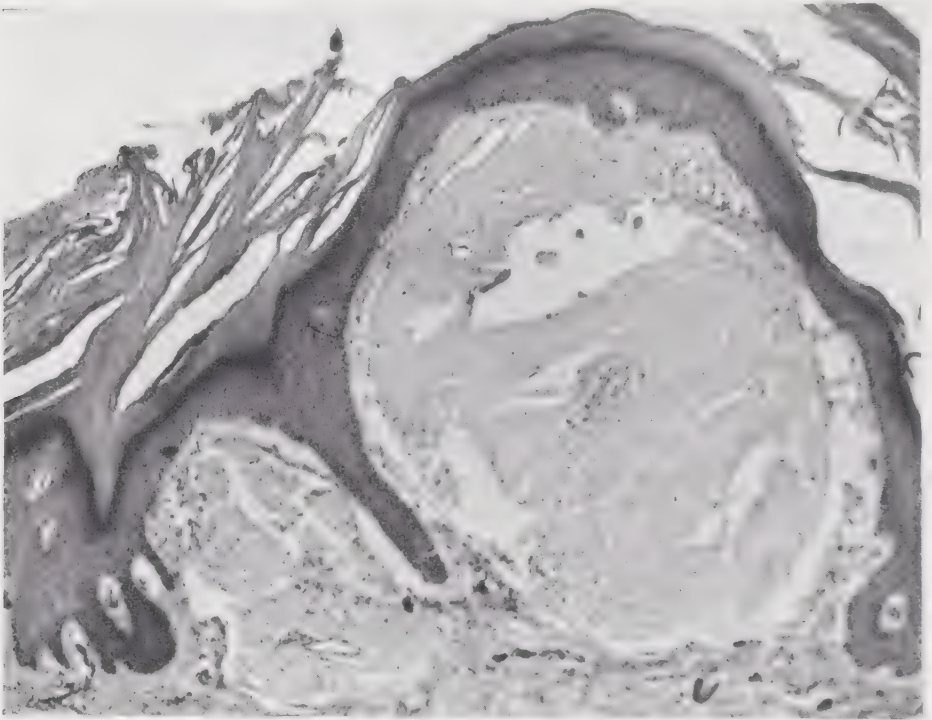


FIG. 75. **Colloid milium.** In the upper dermis, separated from the epidermis by a narrow zone of normal collagen, there are two large, round spaces incompletely filled with a fissured mass of homogeneous material. This material represents colloid. The colloid contains a moderate number of nuclei. ($\times 100$)

epidermal region. It is assumed by many that colloid represents a form of collagen degeneration. Prakken has observed that collagen, before becoming colloid, passes through the stage of basophilic degeneration. However, it is possible that colloid, like amyloid, represents a deposit rather than a product of collagen degeneration (Percival and Duthie).

The epidermis shows hyperkeratosis and atrophy of the stratum malpighii. Large, nearly round spaces lie close to the epidermis, separated from it by only a narrow zone of normal collagen. These spaces extend through the upper third of the dermis and are sharply demarcated by collagen bundles arranged circularly around them.

They are filled incompletely by a fissured mass of homogeneous-appearing material containing a moderate number of nuclei (Fig. 75). The material, referred to as colloid, usually stains eosinophilic with hematoxylin and eosin, though to a lesser degree than normal collagen. Occasionally, however, it stains faintly basophilic. The fissuring of the colloid is due to fixation and dehydration. The nuclei within the colloid are well preserved and represent fibroblasts. Elastic-tissue stains reveal elastic fibers within the masses of colloid; however, they are fragmented and fewer in number than in normal collagen.

In colloid degeneration of the skin, colloid is present not in superficial, circumscribed foci, but diffusely throughout the dermis (Reuter and Becker).

Differential Diagnosis. Differentiation of colloid milium from amyloidosis (see page 274) requires special staining since these two substances greatly resemble each other morphologically and usually stain alike a pale pink with hematoxylin and eosin. One may use van Gieson's stain which stains colloid yellow and amyloid pink, or methyl violet with which only amyloid is stained.

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11

Bacterial Diseases

IMPETIGO

Impetigo may be caused by streptococci or by staphylococci. Bullae are the primary lesion in either case. In the streptococcal variety, the bullae soon rupture, leaving sharply demarcated erosions which be-

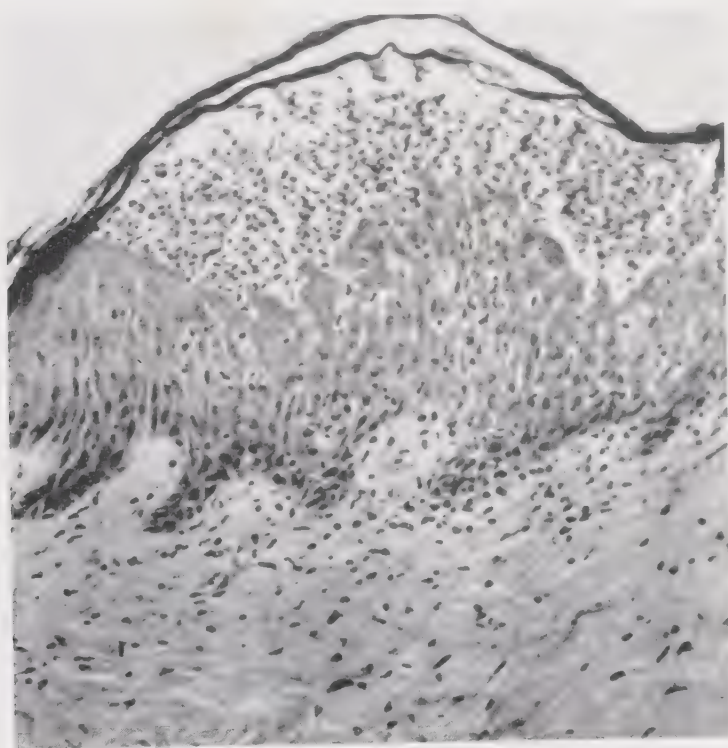


FIG. 76. Impetigo. A subcorneal vesicle filled mainly with neutrophils is present. The epidermis shows spongiosis. Many neutrophils are seen migrating through the epidermis. ($\times 200$)

come covered with heavy, honey-colored crusts. In the staphylococcal variety, the bullae are more durable and dominate the clinical picture. Staphylococcal impetigo occurs especially in the newborn (formerly also called pemphigus neonatorum).

Histopathology. In both the streptococcal and the staphylococcal variety of impetigo, the bulla arises directly beneath the horny layer

(see "Classification of Bullae," page 64). The bulla contains fibrin, polymorphonuclear leukocytes and some lymphocytes (Fig. 76). With Giemsa's or Gram's stain, groups of cocci can be recognized within the bulla. They may lie extracellularly or within neutrophils.

The stratum malpighii underlying the bulla shows spongiosis; many neutrophils can be seen migrating through it. The upper dermis contains a moderately severe inflammatory infiltrate of neutrophils and lymphocytes.

At a later stage, when the bulla has ruptured, the horny layer is absent, and a crust composed of fibrin and neutrophils may be found resting on the stratum malpighii.

ERYSIPELAS

Erysipelas is a localized acute inflammation of the skin caused by streptococci. It is characterized by the presence of well-demarcated, dusky-red areas with or without edema and vesiculation. A typical sign is the advancing, red, raised and indurated border.

Histopathology. The dermis shows marked edema and dilatation of lymphatics and capillaries. When the edema is intense, subepidermal bullae may be present. There is a marked diffuse infiltrate extending throughout the dermis and, occasionally, into the subcutaneous fat. It is composed chiefly of polymorphonuclear leukocytes and some lymphocytes. If sections are stained with Giemsa's or Gram's stain, streptococci are found, chiefly in the lymphatics, but also distributed in the tissue.

FOLLICULITIS (IMPETIGO BOCKHART, FURUNCLE, FOLLICULITIS BARBAE)

Pustular folliculitis may occur in three forms: as impetigo Bockhart, as furuncle and as folliculitis barbae (sycosis vulgaris). All three are caused by staphylococci.

Impetigo Bockhart represents a superficial pustular folliculitis and is characterized by an eruption of pustules, many of which are pierced by a hair.

A furuncle is a deep-seated folliculitis leading to a perifollicular cellulitis and terminating in suppuration and necrosis.

Folliculitis barbae is a deep-seated folliculitis peculiar to the bearded region. At first there are follicular papules and pustules which are followed by diffuse erythema, crusting and infiltration of the skin. Abscesses may be present or absent.

Histopathology. These three diseases cannot always be differentiated on a histologic basis.

IMPETIGO BOCKHART presents a subcorneal pustule situated in the opening of a hair follicle. The upper portion of the hair follicle is surrounded by a considerable inflammatory infiltrate containing varying numbers of polymorphonuclear leukocytes.

A **FURUNCLE** presents, on histologic examination, a perifollicular abscess composed of a dense mass of polymorphonuclear leukocytes with a few lymphocytes. The hair with its follicle and its sebaceous glands is destroyed in the process.

In **FOLLICULITIS BARBAE**, the perifolliculitis is, as a rule, less acute than in furunculosis and does not necessarily result in a perifollicular abscess. Frequently, the infiltrate around the follicle contains relatively few polymorphonuclear leukocytes, but consists mainly of lymphocytes, plasma cells and histiocytes. Some of the sebaceous glands undergo destruction, but the hair follicles may escape destruction. Foreign-body giant cells frequently are present around the hair follicles and the remnants of sebaceous glands. In many cases, instead of being limited to the vicinity of the follicles, the infiltrate extends through the entire upper dermis.

FOLLICULITIS KELOIDALIS (DERMATITIS PAPILLARIS CAPITULI)

Folliculitis keloidalis represents a chronic folliculitis resulting in keloidal scarring. It occurs on the nape of the neck in men. In early cases, one observes follicular papules, pustules and, occasionally, abscesses. The lesions are replaced gradually by fibrous nodules.

Histopathology. Early lesions show the same histopathologic picture as that of a furuncle. Older lesions show chronic granulation tissue containing numerous plasma cells as well as lymphocytes and fibroblasts. Occasionally, foreign-body giant cells are present around remnants of the follicular epithelium. Ultimately, the histologic picture is the same as in keloid, showing bundles of hypertrophic and sclerotic collagen.

HIDRADENITIS SUPPURATIVA

Hidradenitis suppurativa represents a chronic staphylococcal infection of the apocrine glands in the axillary or the pubic regions. Early lesions consist of red, tender nodules, which become fluctuating and finally discharge pus. Ulcers may develop and healing takes place with considerable scarring.

Histopathology. The infection enters by way of the follicles and excretory ducts of the apocrine glands. The earliest cellular reaction is encountered in the subcutaneous tissue within and around the

lumina of apocrine glands. The infection extends through the subcutaneous fat by way of the lymphatics to other apocrine glands as well as to eccrine glands. The lymph vessels are distended and contain many leukocytes and clumps of cocci. In the early stage, the infiltrate is composed predominantly of neutrophils. Later on, lymphocytes and plasma cells predominate and foreign-body giant cells may be present. The upper parts of the dermis and the epidermis are not involved until extensive destruction has occurred throughout the subcutis.

PYODERMA GANGRENOSUM (CHRONIC UNDERMINING BURROWING ULCER)

Pyoderma gangrenosum begins with cutaneous abscesses which break down, forming ulcers. The ulcers spread peripherally. The advancing border of the ulcers is purplish red, edematous and undermined. The condition is associated not infrequently with ulcerative colitis.

Histopathology. The histologic appearance is not diagnostic. In the region of the ulcer, the epidermis is absent. The upper dermis shows necrosis and is permeated by an acute inflammatory infiltrate. Farther down, the infiltrate is chronic inflammatory, granulomatous in nature, consisting of lymphocytes, neutrophils, plasma cells, histiocytes and fibroblasts. Epithelioid cells and foreign-body giant cells may be present. The number of blood vessels is increased throughout the dermis and many vessels show proliferation of their endothelium. The infiltrate may extend deeply into the subcutaneous layer. In areas of healing, fibrosis occurs.

The epidermis at the edge of the ulcer often shows considerable proliferation, so that the histologic picture of pseudo-epitheliomatous hyperplasia (see page 334) may result. Intra-epithelial abscesses may occur in this region.

Differential Diagnosis. Any ulcer, whatever its genesis, may present the histologic picture just described. If the biopsy specimen is taken from an area in which the epidermis shows marked hyperplasia, differentiation from bromoderma may be impossible, since bromoderma too shows marked epithelial hyperplasia and intra-epithelial abscesses.

SUBACUTE BACTERIAL ENDOCARDITIS

Three types of cutaneous lesions may occur in subacute bacterial endocarditis: petechiae, Osler nodes and Janeway lesions (Libman and Friedberg).

Osler nodes are erythematous, slightly raised, tender intracutaneous nodes, averaging 5 mm. in size. They occur most frequently on the fingertips and, as a rule, last 4 or 5 days.

Janeway lesions are small macular or papular lesions, measuring from 1 to 4 mm. in diameter. They are usually red but may be partially hemorrhagic. They occur most commonly on the palms and the soles. Unlike Osler nodes, they are never tender.

Histopathology. The petechiae show the histologic picture of an inflammatory purpura (see page 127), presenting severe vasculitis in addition to the extravasation of red cells. One observes marked endothelial proliferation of capillaries, leading to narrowing or even obliteration of the lumina. An infiltrate composed of polymorphonuclear leukocytes, lymphocytes and histiocytes surrounds and invades the capillaries. Streptococci have never been found in the lesions (Merklen and Wolf; Cornil, Mosinger and Jouve).

The Osler nodes show involvement not only of the capillaries but also of the dermal arterioles and venules which show intense endothelial proliferation and, not infrequently, partial or complete occlusion of their lumina by secondary thrombosis. A dense infiltrate of polymorphonuclear leukocytes, lymphocytes and histiocytes is present in the walls of the vessels and in the perivascular areas. The center of the node may show necrosis. Extravasation of erythrocytes is absent (Cornil, Mosinger and Jouve).

The Janeway lesions resemble the petechiae in their histologic appearance, except that extravasation of erythrocytes is less evident.

MENINGOCOCCEMIA (WATERHOUSE-FRIDERICHSEN SYNDROME)

In fulminating septicemic infections with *Neisseria meningitidis*, purpura is common. Death may occur within from 12 to 24 hours with few or no signs of meningeal involvement. On autopsy, hemorrhages are found not only in the skin but also in the internal organs. Massive bilateral adrenal hemorrhage is a frequent finding.

Occasionally the Waterhouse-Friderichsen syndrome occurs in septicemic infections with organisms other than *Neisseria meningitidis*, such as *Streptococcus hemolyticus* and *Pseudomonas aeruginosa* (*B. pyocyaneus*).

Histopathology. The purpura of meningococcemia is caused by degeneration and inflammatory invasion of the walls of blood vessels (vasculitis) (see page 127). The vessels are dilated, engorged with blood and frequently thrombosed. The endothelial cells are swollen and desquamating, and the vessel walls show necrosis. Polymorphonu-

clear leukocytes are found in the damaged vascular walls as well as perivascularly. Large and small areas of hemorrhage are present in the tissue.

Meningococci can be demonstrated in the cytoplasm of endothelial cells and polymorphonuclear leukocytes. They are also found free in the lumina of vessels and in the perivascular spaces. In addition, the thrombi frequently contain meningococci. Although these organisms can be recognized in routine stains, they are best demonstrated by Giemsa stain.

KERATOSIS BLENNORRHAGICA (GONORRHEAL KERATOSIS)

Keratositis blennorrhagica occurs in chronic gonorrhea, usually in association with urethral discharge and polyarthritis. The lesions have a predilection for the palms, the soles, and the glans penis. Early lesions are represented by pustules. Gradually, the lesions become covered with thick, horny crusts. Confluence of neighboring lesions leads to the formation of extensive horny excrescences, which have been compared with mountain ranges on a relief map.

Reiter's disease, which in typical cases consists of the triad of urethritis, arthritis and conjunctivitis, may present cutaneous lesions identical with those of keratositis blennorrhagica, but gonorrhea is not the cause of the disease.

Histopathology. The first histologic changes consist of the appearance of an acute inflammatory infiltrate in the dermis and the formation of pustules in the uppermost epidermis (Carr and Friedman; Epstein and Chambers). As a rule, the pustules are spongiform (Fig. 77) (Kogoj) as in acrodermatitis continua and in impetigo herpetiformis (see pages 102 and 104). The spongiform appearance of the pustules is caused by the presence of neutrophils inside of edematous, degenerated epidermal cells, whose cellular membranes traverse the pustule like the network of a sponge (Fig. 78).

Simultaneously with, or shortly after, the formation of the pustules, the rete ridges become elongated. At this stage, the histologic picture is indistinguishable from that of acrodermatitis continua.

However, as the lesions age, the parakeratotic horny layer thickens to a degree that is not observed in acrodermatitis continua and is typical of keratositis blennorrhagica. The greatly thickened horny layer is the anatomic substrate for the "mountain-relief appearance" of the lesions observed clinically. The horny layer may measure several millimeters in thickness. It consists of parakeratotic cells intermingled with neutrophils (Fig. 77).

In old lesions, no pustulation remains and the greatly thickened horny layer consists largely of fully keratinized cells with only a few areas of parakeratosis (Herold and Smith).

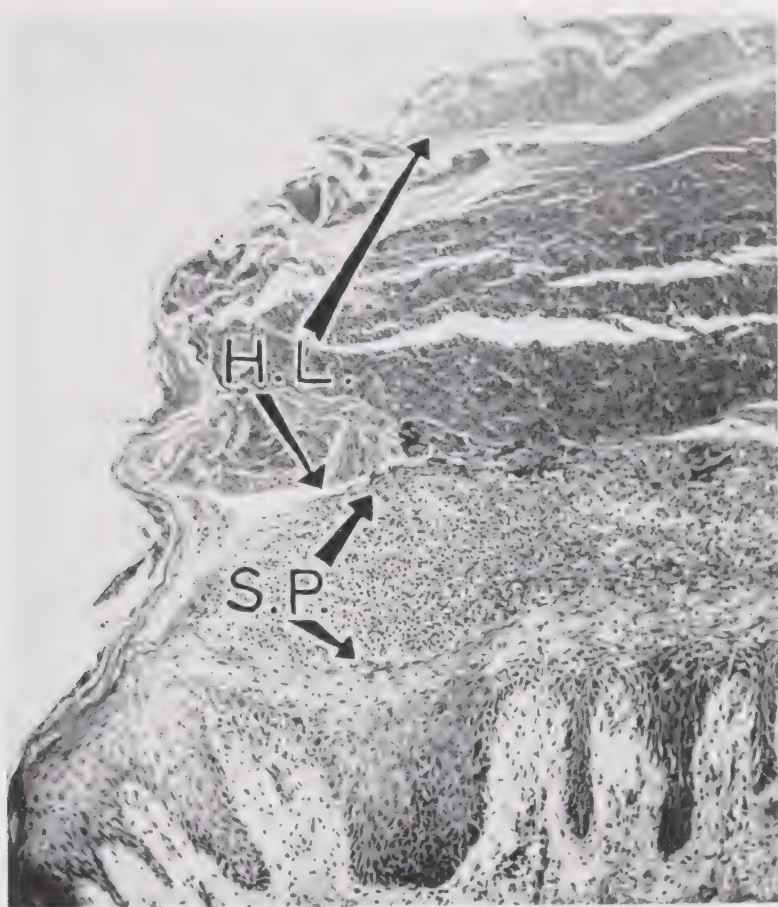


FIG. 77. Keratitis blennorrhagica, late stage. Low magnification. There is a very thick parakeratotic horny layer (H.L.) permeated by numerous neutrophils. The upper stratum malpighii is the seat of a spongiform pustule (S.P.). The spongiform appearance is caused by the preservation of the cellular membranes of epidermal cells within the pustule. There are elongation of the rete ridges and edema of the papillae. ($\times 100$)

Gonococci can be demonstrated only rarely in the lesions of keratitis blennorrhagica. Miale and Singletary found that, out of a total of 115 cases reported in the literature, Gram-negative diplococci were demonstrated in tissue sections in 6 cases, and in smears from the lesions in 5. Only one case is on record in which gonococci were recovered on direct culture of the lesions (Margolin). It is likely that many of the cases reported in the literature as keratitis blennor-

rhagica were nongonorrheal and represented instances of Reiter's disease (Kuske).

In REITER'S DISEASE, the histologic picture is the same as in keratosis blennorrhagica (Lever and Crawford).

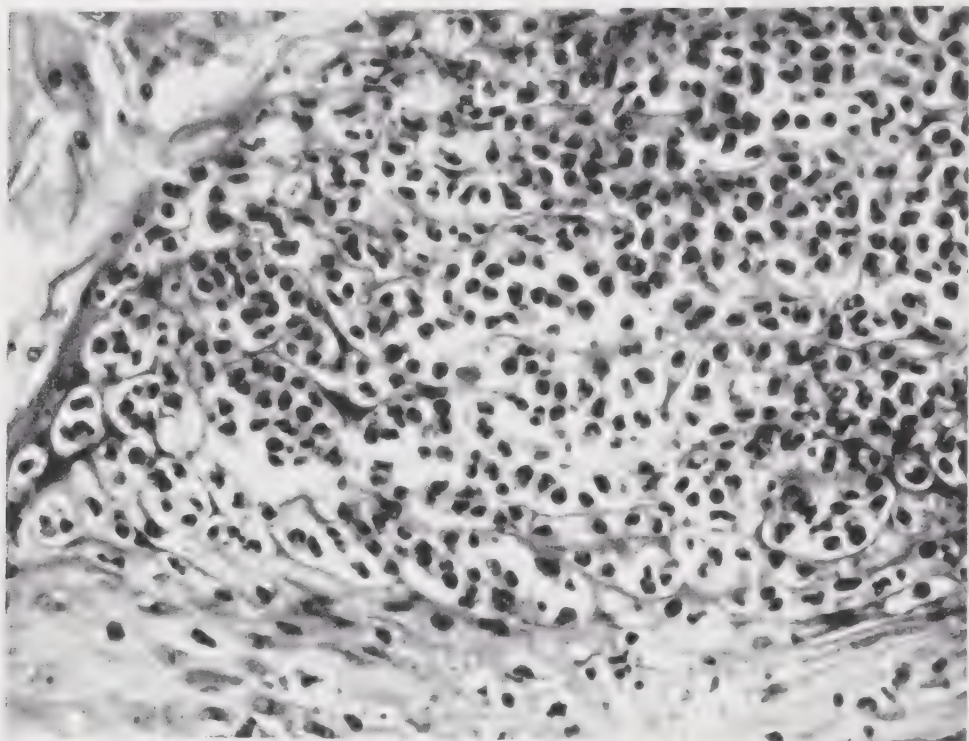


FIG. 78. Keratosis blennorrhagica, late stage. High magnification of Figure 77. The spongiform nature of the pustule is well apparent. ($\times 400$)

TUBERCULOSIS

When a normal, not previously infected guinea pig is inoculated intracutaneously with an adequate dose of tubercle bacilli, a hard nodule develops at the site of inoculation after from 8 to 12 days. The nodule soon ulcerates. The regional lymph nodes become enlarged and sometimes ulcerate (Ghôn complex). Histologic examination of the primary ulcer from 10 to 14 days after inoculation reveals a marked inflammatory response with many polymorphonuclear leukocytes and tubercle bacilli. During the next 2 weeks, the histologic picture changes. Lymphocytes and epithelioid cells appear and replace the polymorphonuclear leukocytes. Distinct tubercles or tuberculoid structures develop at the site of inoculation, and in the regional lymph nodes as well, within 3 to 4 weeks after the inoculation. Simultaneously with the appearance of epithelioid cells, the number of tubercle bacilli decreases rapidly (Sulzberger).

A typical tubercle consists of an accumulation of epithelioid cells surrounded by a wall of lymphocytes. Usually a few Langhans giant cells are present among the epithelioid cells. The epithelioid cell center of the tubercle may show various degrees of caseation. If such typical tubercles are present, one speaks of a tuberculous infiltrate. Frequently, however, in tuberculosis one does not find typical tubercles but only irregular accumulations of epithelioid cells within an inflammatory infiltrate, with or without caseation, and with or without Langhans giant cells. In that case, one speaks of a tuberculoid infiltrate.

It is important to realize that a tuberculous, and particularly a tuberculoid, infiltrate does not necessarily mean tuberculosis. Either may occur in many other diseases, particularly syphilis, leprosy and several of the deep fungus infections. The Jadassohn-Lewandowsky law states that, wherever micro-organisms or their products are being overcome or neutralized by the local immunobiologic reactions, tubercles or tuberculoid structures have a tendency to appear.

Of interest is the work of Sabin, who found, by intracutaneous injections of various fractions of tubercle bacilli, that the protein fraction evokes the necrotizing and lymphocytic response and the phospholipid fraction evokes the epithelioid-cell response.

The histologic diagnosis of the various types of cutaneous tuberculosis is dependent on the correlation of the degree of caseation necrosis, the amount of inflammatory infiltrate, the degree of vascular changes and the relationship of the tubercles to blood and lymph vessels.

Caseation necrosis is so called because of the cheesy macroscopic appearance of the affected tissue. Microscopically, areas of caseation necrosis show complete loss of their architectural outline. One observes eosinophilic granular material in which, unless the caseation necrosis is far advanced, some nuclei are still present. However, most of the nuclei show pyknosis (shrinkage) or karyorrhexis (fragmentation). In local tuberculous infections, caseation necrosis is caused by the action of bacterial toxins alone. In hematogenous infections, obliterative changes in the vessels are responsible in part. If any marked inflammatory infiltrate is absent in lesions of tuberculosis, it is indicative of either a relative resistance of the host or of an attenuated infection.

No generally accepted classification of tuberculosis of the skin exists. The classification presented in Table 3 is based on the classifications offered by Montgomery and by Laymon and Michelson.

TABLE 3.—CLASSIFICATION OF TUBERCULOSIS OF THE SKIN

	AMOUNT OF CASEATION
1. <i>Primary tuberculosis:</i>	
a. Localized infection: tuberculous chancre	Considerable
b. Hematogenous disseminate infection: generalized miliary tuberculosis of the skin	Considerable
2. <i>Reinfection tuberculosis:</i>	
a. Localized infection	
(1) Lupus vulgaris	Slight
(2) Tuberculosis verrucosa cutis	Moderate
(3) Scrofuloderma	Considerable
(4) Tuberculosis cutis orificialis	Considerable
b. Hematogenous disseminate infection: tuberculids	
(1) Micropapular tuberculid: either purely papular or rosea-like (Lewandowsky)	None
(2) Lupus miliaris disseminatus faciei	Slight
(3) Papulonecrotic tuberculid	Considerable
(4) Lichen scrofulosorum	None
(5) Erythema induratum	Considerable

1. PRIMARY TUBERCULOSIS

Primary infection with tuberculosis usually takes place in childhood. It occurs only very rarely on the skin. In the vast majority of cases, it presents itself in the lung as the so-called Ghon complex or primary complex. This consists of a small, caseous lesion at the periphery of one lung with caseation of the regional hilar lymph nodes. The Ghon complex does not become chronic. It either heals or extends rapidly. Extension may be by continuity or by hematogenous dissemination. In the latter case, miliary tuberculosis may develop.

A. TUBERCULOUS CHANCRE

Primary infection of the skin with tuberculosis is more apt to occur in children but may be seen in adults (Michelson, 1935). The cutaneous lesion usually consists of a crust-covered ulcer. It is referred to as tuberculous chancre or primary inoculation tuberculosis of the skin. The regional lymph nodes are enlarged and may or may not suppurate and produce draining sinuses.

Histopathology. The histologic development of the lesion is very much like that observed in experimental cutaneous inoculation of the guinea pig with tubercle bacilli (see page 174). During the early

stage of the disease, the histologic picture is that of a banal, acute, inflammatory reaction, with ulceration and areas of caseation necrosis. Numerous tubercle bacilli are present, particularly in the areas of necrosis. After from 3 to 6 weeks, a more specific histologic picture develops. Epithelioid and Langhans giant cells are then present, though typical tubercles do not form, as a rule. Caseation necrosis remains a prominent feature. At this stage, the number of tubercle bacilli is so greatly decreased that it may be impossible to demonstrate them in histologic sections and the only proof of their presence is through positive animal inoculation experiments. Simultaneously with the decrease in the number of tubercle bacilli in the lesion, the tuberculin test, previously negative, becomes positive. The histologic picture in the regional lymph nodes is identical with that of the cutaneous lesion (O'Leary and Harrison).

B. GENERALIZED MILIARY TUBERCULOSIS OF THE SKIN

The cutaneous lesions are usually papules but may be vesicles or pustules. They tend to break down and form small ulcers.

Histopathology. In early lesions, one observes a nonspecific inflammatory infiltrate with foci of necrosis but without tuberculoid reaction. Numerous tubercle bacilli are found within the blood vessels and in the foci of necrosis. At a later stage, tuberculoid formations may be encountered (Wise).

2. REINFECTION TUBERCULOSIS

The immunity acquired by the primary infection almost always protects, at least for several years. After such a latent period, reinfection may occur. Reinfection tuberculosis usually is mono-organic, so that in cases in which the skin is affected other organs are, as a rule, free from active tuberculosis. As in primary tuberculosis, the infection of the skin may be localized or disseminate.

A. LOCALIZED INFECTION

In localized infections one may find, depending on the virulence of the bacilli and the degree of resistance of the host, either a slight amount of caseation, as in lupus vulgaris, a moderate amount of caseation, as in tuberculosis verrucosa cutis, or a considerable amount of caseation, as in scrofuloderma and tuberculosis cutis orificialis.

(1) *Lupus Vulgaris*

In lupus vulgaris, the lesions, which are found most commonly on the face, consist of sharply demarcated, reddish brown patches containing pinhead-sized, deep-seated nodules. If the blood is pressed

out of the skin by pressure with a glass slide (diascopy), the nodules stand out clearly as yellowish brown macules. Because of their yellowish brown color, the nodules are referred to as apple-jelly nodules. In the course of time, as a rule, the affected areas become atrophic, with contraction of the tissue. However, some areas may show ver-

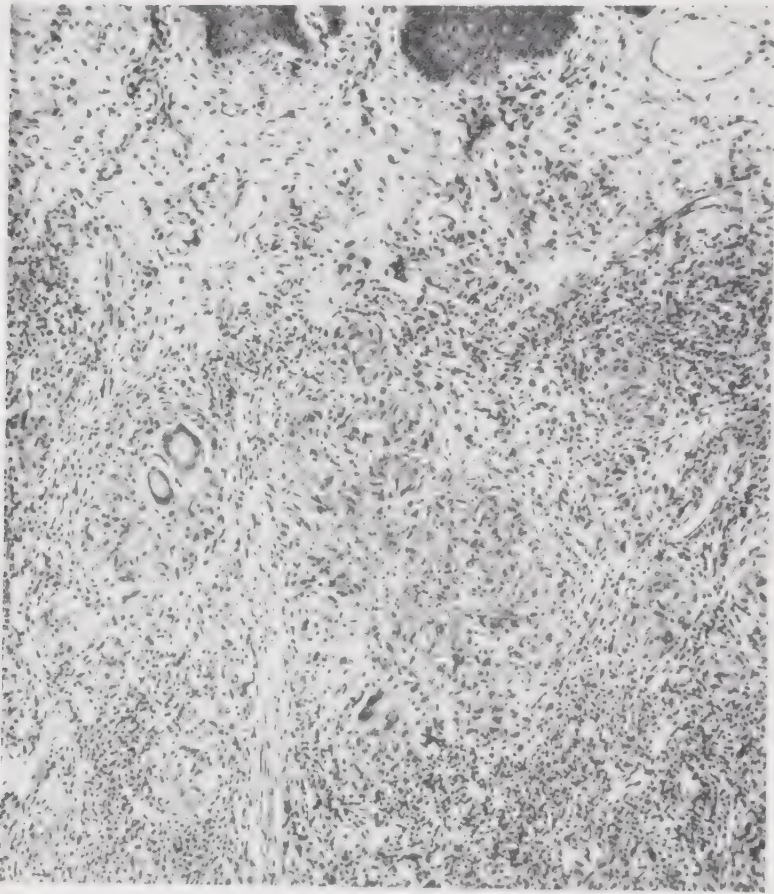


FIG. 79. *Lupus vulgaris*. Low magnification. There are several tubercles. The large tubercle in the center shows slight caseation necrosis. ($\times 100$).

rucous thickening (*lupus vulgaris verrucosus*) or superficial ulceration. Squamous-cell carcinoma may develop at the margin of the ulcers.

Histopathology. Typical tubercles with epithelioid cells, giant cells and a peripheral zone of lymphocytes are present. Caseation necrosis within the tubercles is slight and may be absent. (Figs. 79 and 80.) The amount of inflammatory infiltrate composed of lymphocytes and plasma cells varies. In some cases, the inflammatory infiltrate dominates the histologic picture so that one has to search for occasional tubercles; in other cases, it is slight.

The infiltrate of lupus vulgaris is most pronounced in the upper dermis but in some areas may extend into the subcutaneous layer. It causes destruction of the cutaneous appendages. In areas of healing, extensive fibrosis occurs.

Secondary changes in the epidermis are common. In some areas, the epidermis may show acanthosis, hyperkeratosis and even papil-

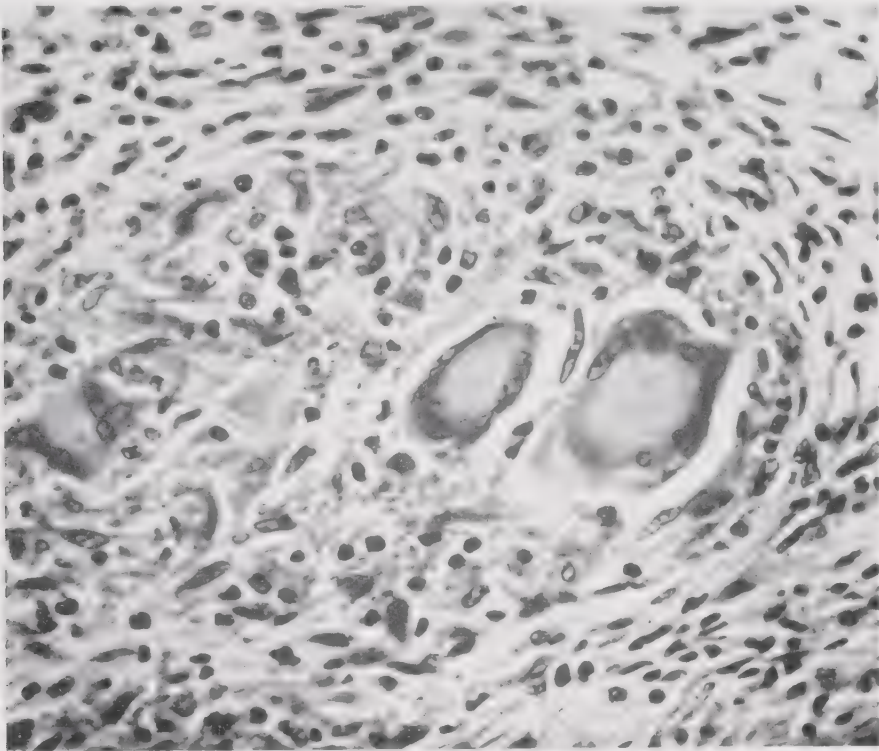


FIG. 80. *Lupus vulgaris*. High magnification of Figure 79. A tubercle containing several Langhans giant cells is shown. The nuclei of the giant cells lie in "horseshoe arrangement." ($\times 400$)

lomatosis (*lupus vulgaris verrucosus*). In other areas, by the pressure of the infiltrate, atrophy and even destruction of the epidermis may occur, resulting in ulceration and secondary pyogenic infection. At the margin of such ulcers, pseudo-epitheliomatous hyperplasia and, in some instances, squamous-cell carcinoma may be found.

Tubercle bacilli are present in such small numbers that their presence can hardly ever be demonstrated by staining methods. Guinea-pig inoculation, on the other hand, usually gives a positive result.

Differential Diagnosis. Differentiation from sarcoidosis may be very difficult and occasionally is impossible. No absolute histologic criterion exists by which the two diseases can be differentiated with certainty. As a rule, however, the infiltrate in sarcoidosis tends to

lie in scattered islands throughout the dermis, while in lupus vulgaris the infiltrate tends to be compact and to lie mainly in the upper dermis. Furthermore, sarcoidosis usually shows much less lymphocytic reaction, more fibrosis around the nests of epithelioid cells, a smaller number of giant cells and complete absence of necrosis (Ronchese). The epidermis in sarcoidosis is either normal or shows pressure atrophy, while in lupus vulgaris, in addition to atrophy, there may be areas of ulceration, acanthosis and pseudo-epitheliomatous hyperplasia. However, the only laboratory procedure by which the two diseases can be differentiated with certainty is guinea-pig inoculation, which usually is positive in lupus vulgaris, always negative in sarcoidosis.

For a discussion of swimming-pool granuloma, which is thought by some to be an "inoculation lupus vulgaris," see page 142.

(2) *Tuberculosis Verrucosa Cutis (Including Verruca Necrogenica)*

This form of tuberculosis represents an infection of a nearly immune skin with virulent tubercle bacilli. The lesions, of which there may be one or several, consist of verrucous, hyperkeratotic areas surrounded by an inflammatory border. Crusts may be intermingled with the keratotic material. Frequently, pus may be expressed from fissures within the verrucous lesion.

Histopathology. The histologic picture shows acanthosis, hyperkeratosis and papillomatosis of the epidermis. Beneath the epidermis there is an acute inflammatory infiltrate of polymorphonuclear leukocytes and lymphocytes with abscess formation. In the middle portion of the dermis, one usually finds typical tubercles with a moderate amount of caseation necrosis. At times, however, only a nonspecific inflammatory infiltrate is present. Tubercle bacilli are more numerous than in lupus vulgaris and, therefore, occasionally can be demonstrated histologically (Montgomery).

(3) *Scrofuloderma (Tuberculosis Cutis Colliquativa)*

Scrofuloderma may originate in the subcutaneous tissue; frequently, however, it represents a direct or lymphatic extension to the skin of an underlying tuberculous focus, located usually in a lymph node or bone. The lesion becomes first manifest as a bluish red painless swelling, which suppurates and later breaks down to form an ulcer with irregular, undermined bluish borders.

Histopathology. The center of the lesion shows nonspecific abscess formation, with ulceration of the epidermis. At the periphery, how-

ever, one sees tubercle formation with marked caseation necrosis and a considerable amount of chronic inflammatory reaction (Fig. 81). The number of tubercle bacilli is usually sufficient to enable one to find them in sections stained after Ziehl-Neelsen (Michelson, 1924).

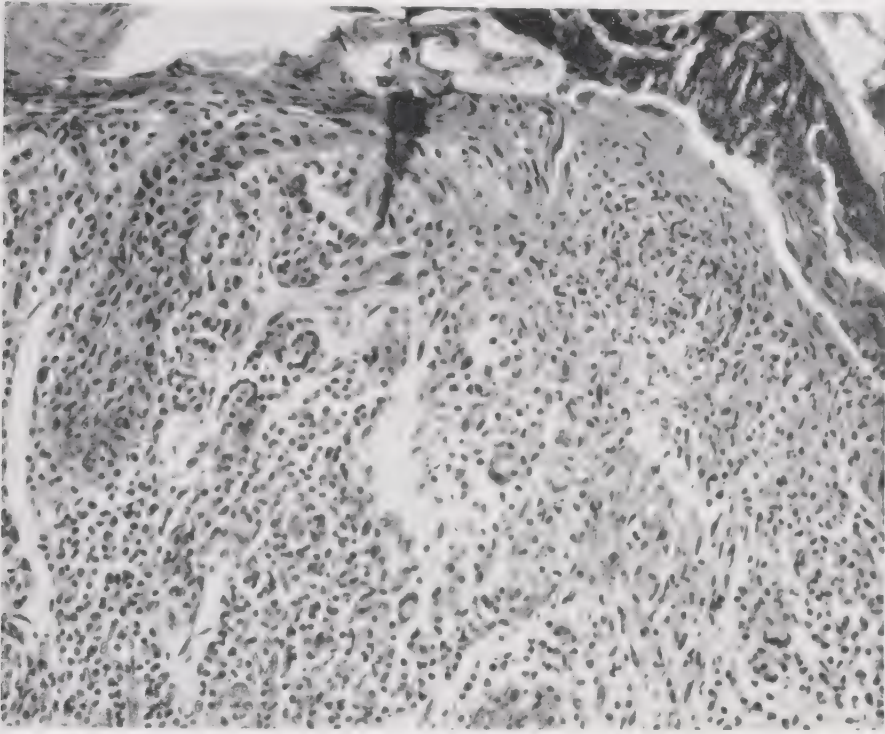


FIG. 81. Scrofuloderma. Margin of an ulcer. On the right side of the photograph one observes necrosis of epidermis and dermis. In the center are tuberculoid structures. On the left, the infiltrate is composed of lymphocytes and plasma cells. ($\times 200$)

Differential Diagnosis. For differentiation from erythema induratum, see page 186, and from gummatous syphilis, see page 215.

(4) *Tuberculosis Cutis Orificialis*

The lesions are shallow ulcers with a granulating base, occurring about the mucous orifices of patients with virulent internal tuberculosis.

Histopathology. The histologic picture may show merely an ulcer surrounded by a nonspecific inflammatory infiltrate. In most instances, however, one finds tubercle formations with caseation necrosis deep in the dermis. The epidermis at the margin of the ulcer may show hyperplasia. Tubercle bacilli usually can be demonstrated in the sections, even when the histologic appearance is nonspecific.

B. HEMATOGENOUS DISSEMINATE INFECTION: TUBERCULIDS

Tuberculids are caused by a hematogenous dissemination of tubercle bacilli in patients possessing a rather high immunity to tuberculosis. Because of the high immunity, the bacilli are rapidly destroyed in the skin and therefore are usually not demonstrable in sections or by animal inoculation. Although, naturally, the hematogenous dissemination must take place from an internal focus, often this focus cannot be found. Clinically as well as histologically, transitions between the various forms of tuberculids occur not infrequently.

(1) *Micropapular Tuberculid (Including Rosacea-like Tuberculid of Lewandowsky)*

The eruption is limited to the face and consists of numerous small, slightly indurated but not elevated papules of about pinhead size.



FIG. 82. Micropapular tuberculid (rosacea-like tuberculid of Lewandowsky). In the center, there is an island of epithelioid cells with only a slight admixture of lymphocytes. This picture is indistinguishable from that of sarcoid. ($\times 100$)

Some of the patients present, in addition, a diffuse erythema of the face. To these cases, the term rosacea-like tuberculid of Lewandowsky has been applied.

Histopathology. Histologically, the papules usually show islands of epithelioid cells with only a few lymphocytes and few or no giant cells; they thus present a picture indistinguishable from that of sarcoidosis (Fig. 82) (Laymon and Michelson). In other cases, a moderate admixture of lymphocytes is present, so that the appearance resembles lupus vulgaris more than sarcoid (MacKee and Sulzberger). Caseation necrosis is absent, as a rule; occasionally, one finds slight central necrosis in the tubercles (Wile and Grauer).

Since the papular type of acne rosacea may show the same histologic picture as the rosacea-like tuberculid of Lewandowsky (Miescher; Laymon) (see page 124), the latter diagnosis should never be made on the basis of the histologic findings alone but only when the following additional criteria exist: (1) presence clinically of minute, lupoid nodules, and (2) concomitant evidence of tuberculosis such as pulmonary tuberculosis or a high degree of tuberculin sensitivity (Laymon). The possibility exists that all cases of rosacea-like tuberculid are instances of acne rosacea, and that cases of micro-papular tuberculid without rosacea-like features represent miliary sarcoidosis.

(2) *Lupus Miliaris Disseminatus Faciei*

Lupus miliaris disseminatus faciei occurs on the face only. The eruption consists of firm, elevated, discrete papules occurring singly or in groups.

Histopathology. The histologic picture shows typical tubercles surrounded by an inflammatory infiltrate. Central caseation is frequent in the tubercles (Fig. 83). Thus, the histologic picture may be compared to that of lupus vulgaris, although, in the latter, caseation is less pronounced.

LICHENOID TUBERCULID. A variant of lupus miliaris disseminatus faciei, with the same histologic picture, has been described by Ockuly and Montgomery under the name lichenoid tuberculid. There is a generalized eruption of discrete or grouped erythematous papules with predominance on the extremities and usually no lesions on the face.

(3) *Papulonecrotic Tuberculid*

The eruption is not limited to the face as it is in the two preceding types. In addition to the face, the extremities and the trunk may be affected. The lesions consist of indolent, inflammatory papules which

come in crops and undergo central necrosis. Papulonecrotic tuberculid occasionally occurs simultaneously with erythema induratum.

Histopathology. One observes a small central area of necrosis involving the superficial dermis and the overlying epidermis. The area

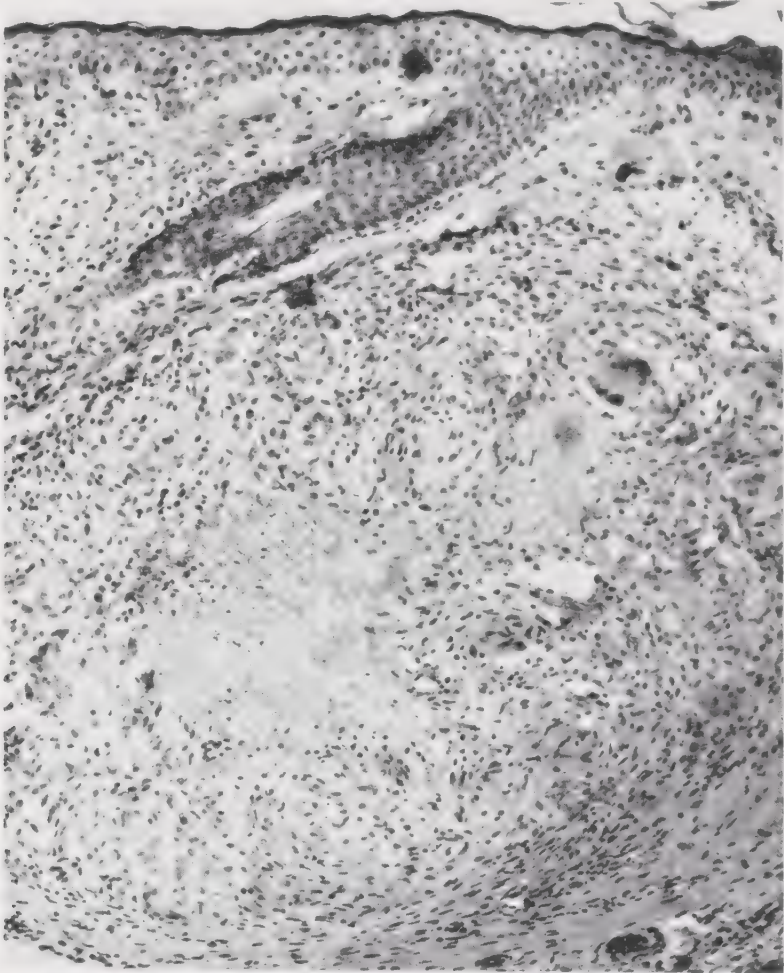


FIG. 83. *Lupus miliaris disseminatus faciei*. A tubercle showing central caseation is present in the dermis. It is surrounded by a moderately severe inflammatory infiltrate. ($\times 100$)

of necrosis is surrounded by a zone of inflammation which is largely nonspecific but may contain at its periphery tubercles showing a moderate amount of caseation necrosis. The infiltrate may extend into the subcutaneous fat. The blood vessels in the lower dermis show obliterative endarteritis and endophlebitis, with thrombosis and recanalization of their lumina. The walls of the vessels may be invaded by inflammatory cells. The vascular lesions are responsible for the

superficial necrosis. The histologic picture may be called a miniature erythema induratum.

(4) *Lichen Scrofulosorum*

The lesions, which occur chiefly on the trunk, consist of indolent, pinhead-sized papules. Their color varies from that of normal skin to a pale red.

Histopathology. The infiltrate consists of almost pure epithelioid tubercles with only an occasional giant cell. A narrow zone of lymphocytes may or may not be present at the periphery of the tubercles. There is no caseation. The infiltrate is located in the upper dermis and frequently, but not invariably, is arranged about hair follicles (Montgomery).

(5) *Erythema Induratum*

Erythema induratum, or tuberculosis cutis indurativa, is a chronic, recurrent eruption occurring on the calves of women. In contrast with the other tuberculids, the presence of tubercle bacilli has been demonstrated repeatedly in histologic sections and by inoculation of guinea pigs (Montgomery, O'Leary and Barker). The lesions consist, at first, of painless, deep-seated, subcutaneous infiltrations. Gradually, the infiltrations extend to the surface, forming bluish red plaques which often ulcerate.

Histopathology. In early lesions, the histologic changes are limited to the lower dermis and the subcutis; occasionally, only the subcutis is involved (Fig. 84). The infiltrate may be largely nonspecific but is distinctly tuberculoid at least in some areas. Sometimes, however, it is necessary to cut deeper into the block of tissue to find such areas.

In areas in which the infiltrate is tuberculoid, one finds epithelioid and giant cells, occasionally in tubercle arrangement (Fig. 85). In areas of nonspecific infiltration, one observes predominantly lymphocytes and plasma cells. Both types of infiltrates invade between the fat cells and gradually replace them (proliferation atrophy or "Wucheratrophie" of fat). Caseation necrosis is nearly always present and may be extensive. In areas of caseation necrosis, the fat cells often are still preserved, while the invading infiltrate between them has been supplanted by an amorphous, finely granular, eosinophilic material in which some pyknotic nuclei are present.

Vascular changes are extensive and usually severe. All sizes of vessels show proliferative changes. The changes are severest in the larger arteries and veins. Their walls become infiltrated with round cells and greatly thickened in all coats. Thrombosis and obliteration result

(Fig. 86). The obliteration results in widespread necrosis and abscess formation. The necrosis may extend to the dermis and the epidermis and lead to ulceration.

Differential Diagnosis. Differentiation from erythema nodosum rarely causes difficulties even though a few small foci of tuberculoid

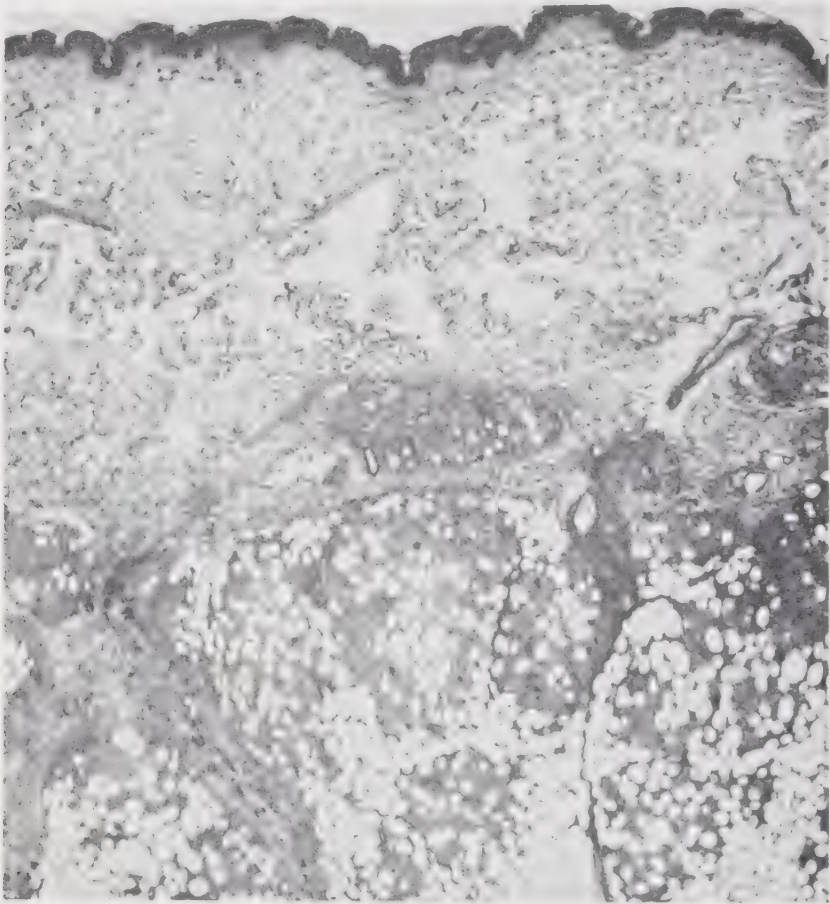


FIG. 84. **Erythema induratum.** Low magnification. The infiltrate is limited to the subcutaneous fat. It invades between the fat cells and gradually replaces them (proliferation atrophy of the fat). ($\times 25$)

infiltrate may occur in erythema nodosum. In the first place, the infiltrate is much more massive in erythema induratum than in erythema nodosum, where it usually consists of small scattered aggregates, and, most important, one usually finds at least a few areas of caseation necrosis which never occurs in erythema nodosum. Furthermore, extensive tuberculoid infiltration and abscess formation do not occur in erythema nodosum either, and, if present, establish the diagnosis of erythema induratum beyond any doubt. Lesions showing a pronounced tuberculoid infiltrate, extensive caseation and ulcera-

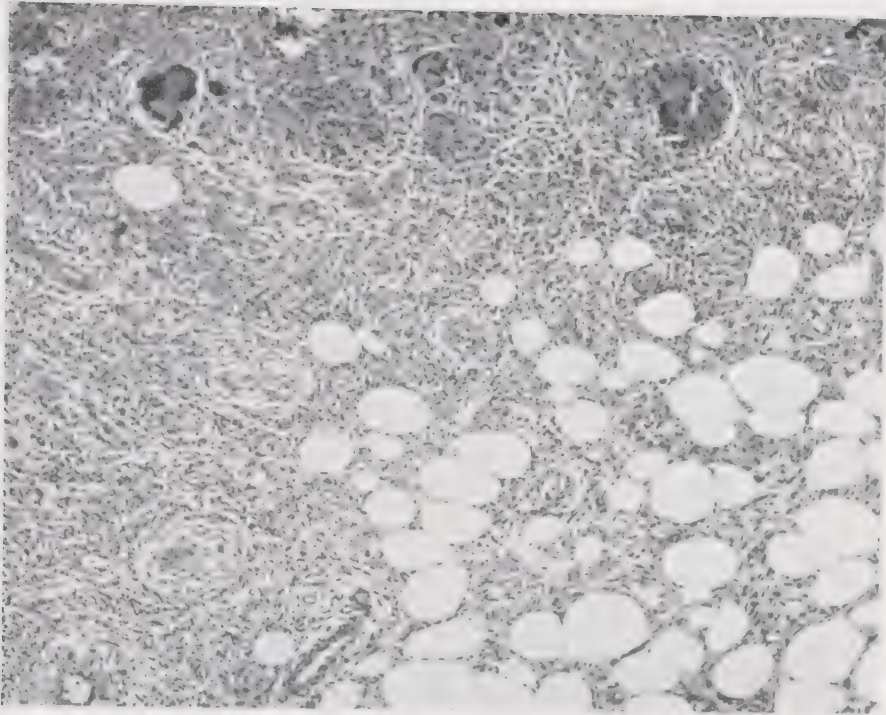


FIG. 85. *Erythema induratum*. High magnification. The infiltrate in the area shown is tuberculoid in appearance being composed largely of epithelioid cells and giant cells. Many of the small vessels show proliferation of their walls. ($\times 200$)

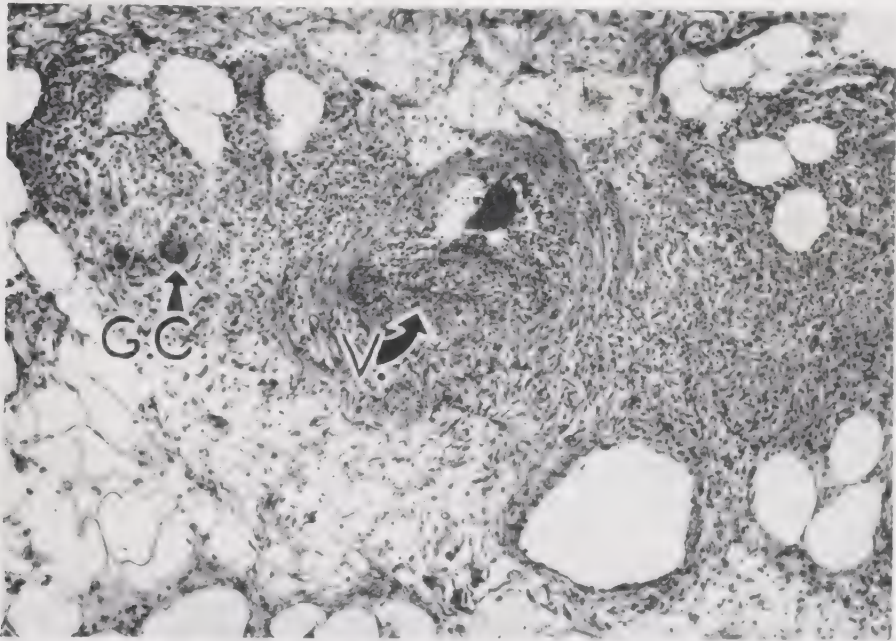


FIG. 86. *Erythema induratum*. High magnification. A large vessel (V.) in the subcutaneous fat is invaded by inflammatory cells and thrombosed. At the right of the vessel, the inflammatory infiltrate is nonspecific; at the left, epithelioid cells and a Langhans type of giant cell (G.C.) are located. ($\times 200$)

tion may resemble scrofuloderma. However, scrofuloderma shows no significant vascular changes and usually shows many tubercle bacilli on staining with Ziehl-Neelsen's stain.

For differentiation from gummatous syphilis, see page 215.

SARCOIDOSIS

Sarcoidosis is a systemic disease which may affect many organs. The skin frequently is involved. Four types of cutaneous sarcoidosis are generally recognized: Boeck's sarcoid, subcutaneous sarcoid of Darier-Roussy, lupus pernio of Besnier and erythrodermic sarcoid. Boeck's sarcoid, the most common type of cutaneous sarcoidosis, is characterized by soft, brownish red intracutaneous papules, nodules or plaques. By central clearing, annular lesions may result. The lesions only rarely ulcerate. Subcutaneous sarcoid of Darier-Roussy shows subcutaneous nodules which often reach several centimeters in diameter and do not break down. The overlying skin is either of normal color or bluish red. Lupus pernio of Besnier presents soft nodules and infiltrated plaques of violaceous color, the surface of which shows numerous telangiectases. Erythrodermic sarcoid is characterized by large, sharply demarcated, slightly scaling, brownish red patches showing little or no infiltration (Lever and Freiman; Wigley and Musso). It might be pointed out that Spiegler-Fendt sarcoid is not sarcoidosis but a lymphoid hyperplasia possibly related to lymphoma (see page 491).

Histopathology. The histologic picture is essentially the same in all four types of cutaneous sarcoidosis. In the skin, as in other organs, it is characterized by the presence of circumscribed islands of epithelioid cells, so-called epithelioid-cell tubercles.

In Boeck's sarcoid, the islands of epithelioid cells are located predominantly in the dermis, while, in Darier-Roussy's sarcoid, they are found mainly in the subcutaneous tissue. In lupus pernio, the histologic picture differs from that of Boeck's sarcoid only by the presence of greatly dilated capillaries in the upper portion of the dermis. In the erythrodermic form, the infiltrate shows rather small foci of epithelioid cells intermingled with histiocytes and lymphocytes in superficial perivascular arrangement (Lever and Freiman; Wigley and Musso).

In active lesions of sarcoidosis, the islands of epithelioid cells contain few Langhans giant cells or none at all (Fig. 87). A slight, and occasionally moderate, admixture of lymphocytes is present, particularly at the margins of the epithelioid-cell islands (Fig. 88). Caseation necrosis is almost always absent. Rarely, some necrosis is found in

the center of the epithelioid-cell islands. If a reticulum stain is employed, one sees a reticulum network surrounding and permeating the islands of epithelioid cells (Fig. 89). The network varies in density. In most areas, the reticulum fibers surround almost every epithelioid cell, but, in others, the fibers are concentrated at the periphery, leaving the central portions relatively free.

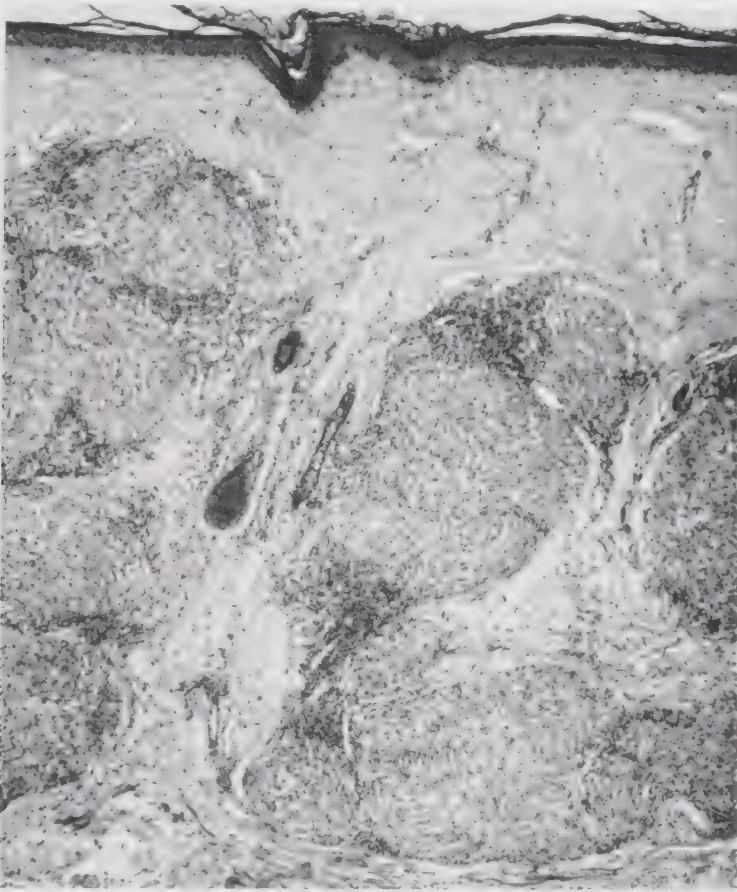


FIG. 87. Sarcoidosis, active stage. Low magnification. There are large islands of epithelioid cells with only a slight admixture of lymphocytes. ($\times 50$)

In the healing phase, one finds increasing fibrosis, usually starting at the periphery of the islands and leading to obliteration of the epithelioid cells and the lymphocytes (Fig. 90). In such lesions, the gradual transformation of reticulum fibers into collagen fibers can be well observed. A moderate number of giant cells is usually present at this stage. They are apt to be large in size and irregular in shape and thus often resemble foreign-body giant cells rather than Langhans giant cells. Occasionally, they contain so-called Schaumann inclusion bodies, which are round or oval, doubly contoured, lami-

nated and often calcified (Schaumann, 1941). In other cases, asteroid inclusion bodies have been found inside of giant cells (Fig. 91) (Lever and Freiman). The significance of the Schaumann and the asteroid inclusion bodies is not known. Neither is specific for sarcoidosis since Schaumann bodies may occur also in berylliosis (see page 141) and asteroid bodies have been observed in other granulomas, especially in foreign-body granulomas.

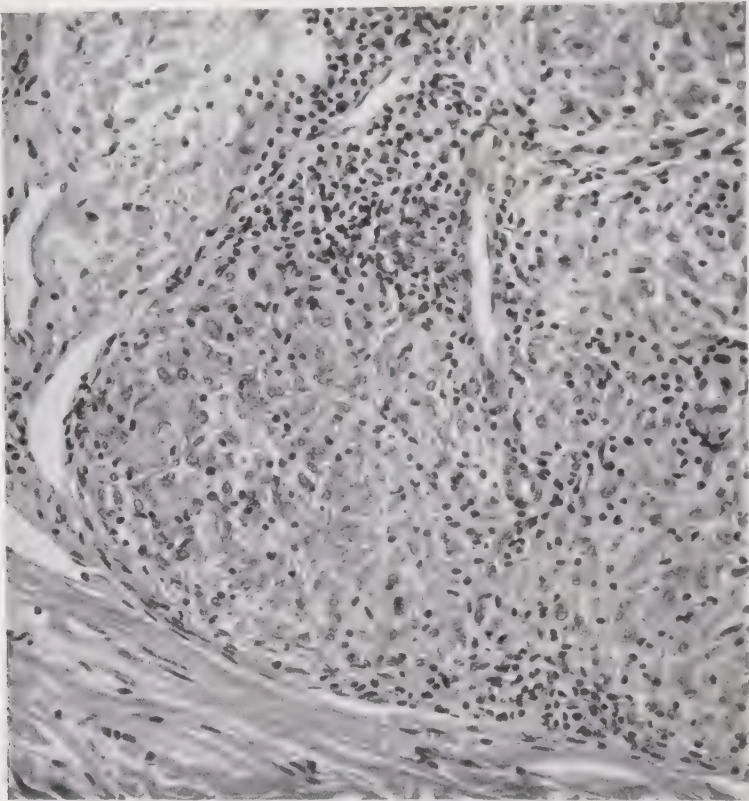


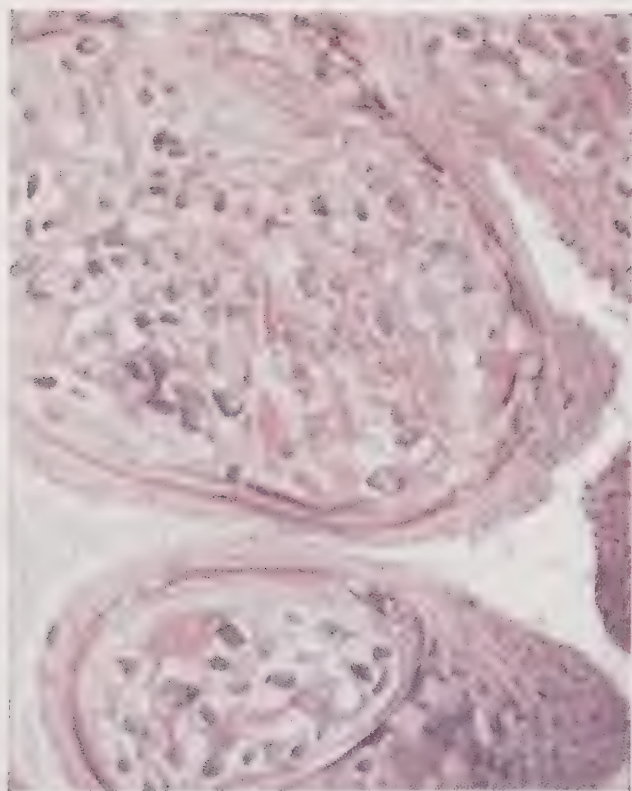
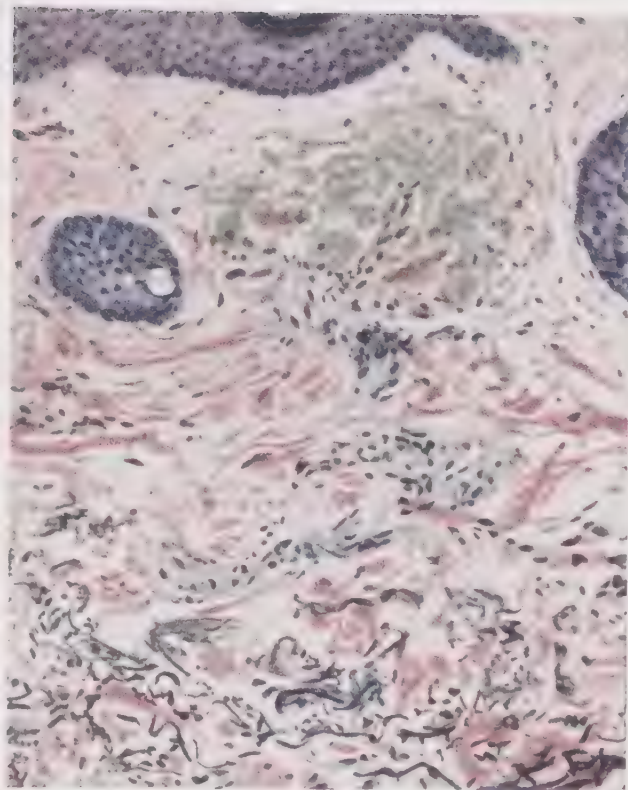
FIG. 88. Sarcoidosis, active stage. High magnification of Figure 87. The island of epithelioid cells is sharply demarcated. A slight lymphocytic infiltrate is present at the margin of the island. Giant cells are absent. ($\times 200$)

Differential Diagnosis. The differentiation of lesions of sarcoidosis from those of lupus vulgaris may be very difficult in cases in which the islands show more than just a slight admixture of lymphocytes (see page 179). A histologic picture identical with that seen in sarcoidosis may occur in the cutaneous granulomas of systemic berylliosis (see page 141) and in tuberculoid leprosy (see page 195). In the latter, however, epithelioid-cell islands usually are found invading and destroying nerves in the dermis and the subcutaneous tissue.

Systemic Lesions. The systemic nature of sarcoidosis, at first not recognized, has been established particularly by Schaumann's work

PLATE 2

Senile degeneration. Basophilic degeneration is present in the upper dermis. The collagen bundles are broken up into amorphous clumps which stain basophilic with hematoxylin and eosin. ($\times 90$)



Molluscum contagiosum. The gradual development of the molluscum bodies in the epidermal cells can be studied. The bodies are largest within the cornified cells located in the center of the lobule. They stand out sharply because of their strongly basophilic staining. ($\times 350$)

(Schaumann, 1936). Numerous organs may be involved (Thomas; Ricker and Clark; Longcope and Freiman). The lymph nodes are frequently, and the tonsils occasionally, involved. In the lungs, foci of sarcoidosis are often present and may, on roentgenologic examination, reveal a picture resembling that of miliary tuberculosis or Hodgkin's disease (McCort, Wood, Hamilton and Ehrlich). The

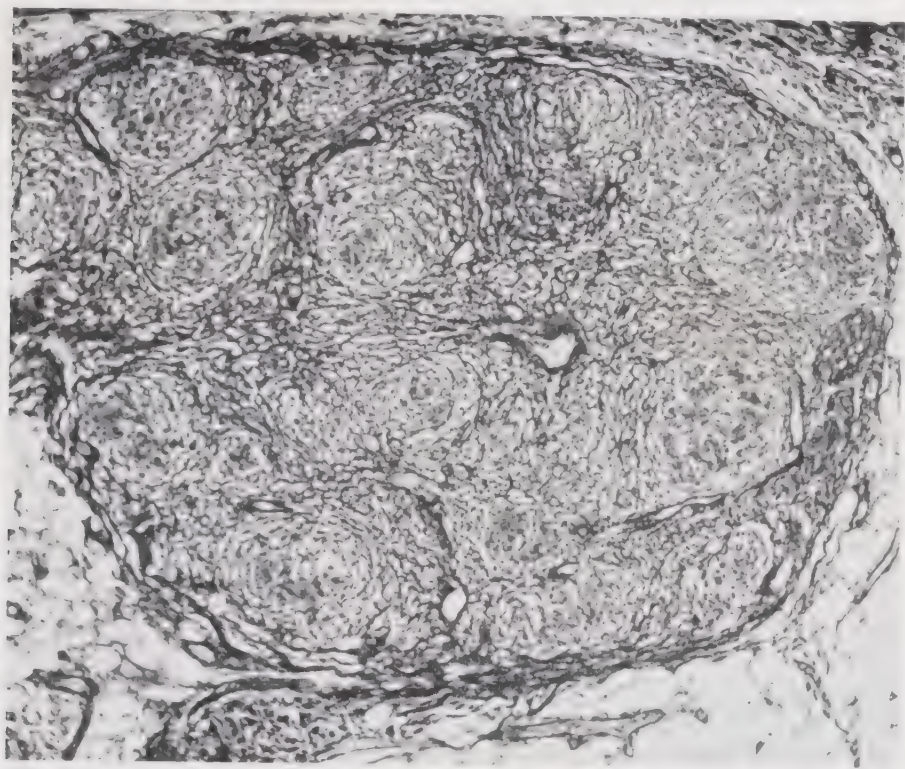


FIG. 89. Sarcoidosis, active stage. Foot's reticulum stain. Reticulum fibers surround and permeate the epithelioid-cell islands. At the margin of the lesions, one can observe the gradual transformation of reticulum fibers into collagen fibers. ($\times 100$)

spleen may be considerably enlarged. The phalanges of the fingers and the toes may show lesions of sarcoidosis, which in roentgenograms look like cysts and formerly were called *ostitis cystica* of Jüngling. Histologically, these lesions represent replacement of bone marrow and bone by sarcoid tissue (Ellis). Uveoparotitis of Heerfordt is also a manifestation of sarcoidosis (Pinner; Michelson). In occasional instances, the heart, the kidneys, the gastro-intestinal tract and the central nervous system are the site of lesions (Longcope and Freiman). Involvement of the lungs, if extensive, of the heart or of the central nervous system may cause death.

Cause. The cause of sarcoidosis is not yet known. Some authors regard it as a noncaseating form of tuberculosis (Pinner). A few

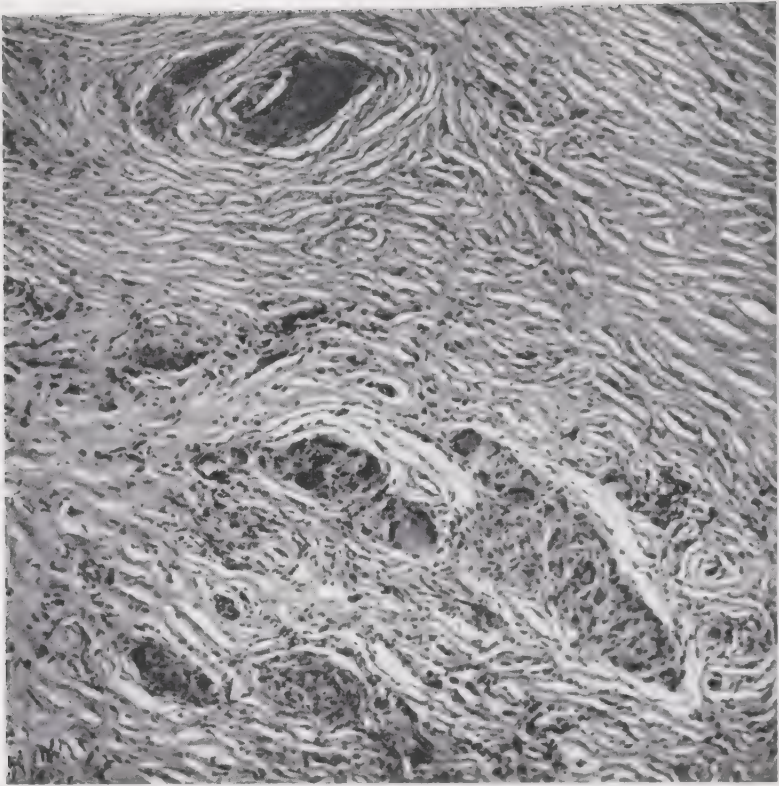


FIG. 90. Sarcoidosis, healing stage. There is considerable fibrosis with progressive obliteration of the epithelioid cells. In contrast with early lesions, giant cells are numerous. ($\times 200$)

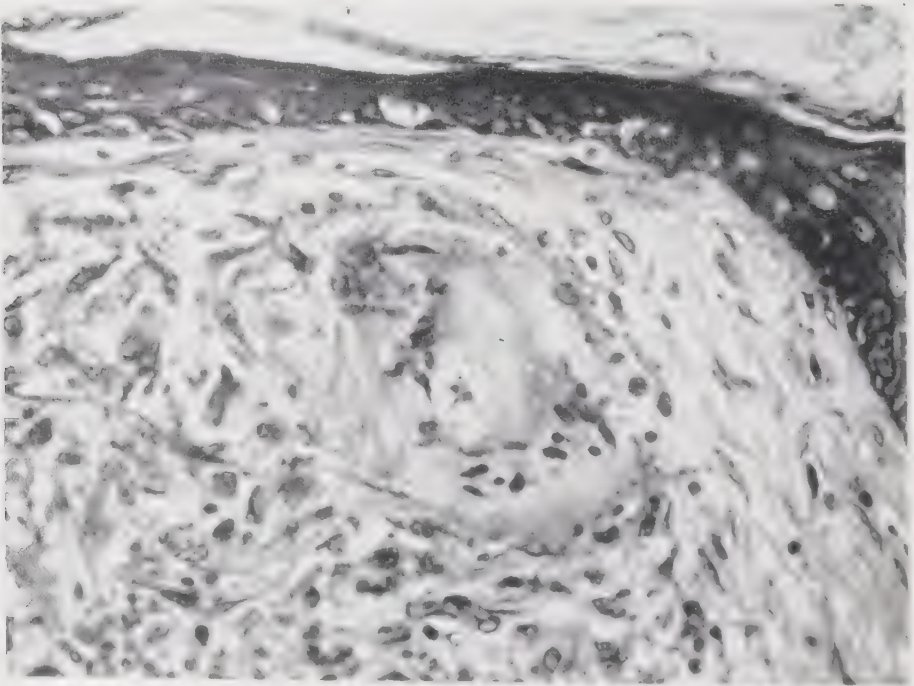


FIG. 91. Sarcoidosis. A large giant cell contains an asteroid inclusion body. ($\times 400$)

authors have reported the finding of tubercle bacilli in lesions of sarcoidosis (Kyrle; Kalkoff and Mohr). It is possible, however, that in such cases either the diagnosis of sarcoidosis was erroneous or a concomitant tuberculosis existed.

If sarcoidosis is due to tuberculosis, it is necessary to assume that the tubercle bacilli are quickly killed and disintegrated under the influence of local immune forces. Under these circumstances, the lipids of the bacillus might be capable of inducing the epithelioid-cell response, whereas the protein of the bacillus, in the absence of hypersensitivity, produces no significant necrosis or constitutional reaction (see page 175). Thus, the same immunologic situation responsible for the prompt killing of the bacilli might explain the morphologic character of the lesion (Freiman).

LEPROSY

Leprosy is caused by the lepra bacillus, *Mycobacterium leprae*, an acid-fast organism.

Three types of leprosy exist: lepromatous leprosy, tuberculoid (or neural) leprosy and indeterminate leprosy (Canizares; Arnold, 1949). The lepromatous and the tuberculoid types are definite clinical, pathologic, bacteriologic and immunologic forms of leprosy. They do not occur together in the same patient and transformation of the lepromatous type into the tuberculoid type, or vice versa, is very rare. Indeterminate leprosy represents a transitional stage. It may remain indeterminate for a long time and then heal or may develop into lepromatous or tuberculoid leprosy. Lepromatous leprosy has a poor prognosis for arrest or recovery, while tuberculoid leprosy has a good prognosis for arrest or recovery. In lepromatous leprosy, the lepromin test is negative because of absence of immunity; in tuberculoid leprosy, it is positive. In indeterminate leprosy, the lepromin test may be positive or negative. Cases of indeterminate leprosy showing a positive test will probably remain indeterminate or will develop tuberculoid lesions; those showing a negative lepromin test, in all probability, will develop lepromatous lesions.

Clinical Appearance. Lepromatous leprosy is characterized by red, elevated, granulomatous infiltrations of the skin, called lepromas. These granulomas occur not only in the skin but also in the mucous membranes of the upper respiratory tract, the eyes, the testes, the superficially located nerves and the reticulo-endothelial structures, such as the lymph nodes, the liver, the spleen and the bone marrow. Neurologic changes, such as anesthesia, trophic disturbances and paralysis, usually are present. Tuberculoid leprosy, also called neural or maculo-anesthetic leprosy, affects mainly the skin and the nerves.

The cutaneous lesions consist of sharply circumscribed, erythematous, often hypopigmented patches or flat infiltrations. Annular configuration is common. The lesions usually are hypoesthetic. The peripheral nerves, especially the ulnar nerve, are thickened and palpable. Anesthesia, trophic disturbances and paralysis occur just as

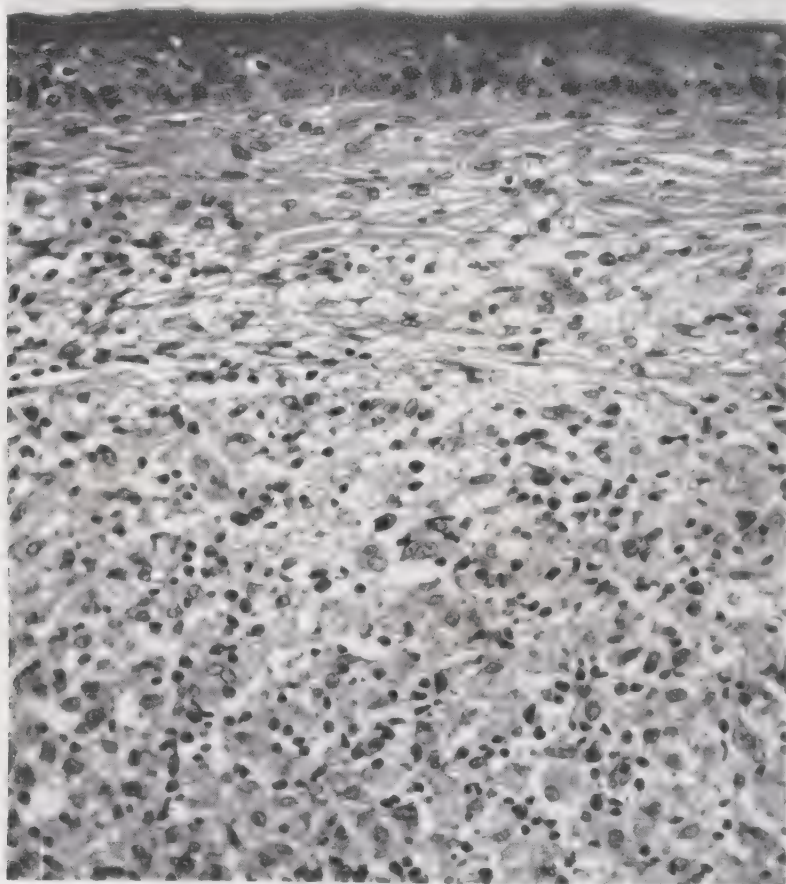


FIG. 92. Lepromatous leprosy, early stage. The granulomatous infiltrate consists predominantly of histiocytes and lepra cells with foamy cytoplasm. ($\times 200$)

in the lepromatous type. Indeterminate leprosy resembles tubercloid leprosy in its clinical manifestations.

Histopathology. Lepromatous leprosy shows a granulomatous infiltrate. It is massive in the upper dermis and focal around the arteries, the veins and the nerves in the lower dermis and the subcutaneous fat. Histiocytes and lepra cells predominate, but, in addition, there are lymphocytes, plasma cells and, in older lesions, fibroblasts (Fig. 92). Lepra cells, or Virchow cells, develop from histiocytes. They are large, foamy cells resembling xanthoma cells. On staining with fat stains, they are shown to contain lipid which, in contrast to

that found in xanthoma, is not doubly refractile (Tilden). On staining with Ziehl-Neelsen or Fite stain, innumerable bacilli are found, particularly inside the lepra cells, where they may lie in bundles (like packs of cigars) or large clumps called globi (Fig. 93). It should be stressed that *Mycobacterium leprae*, unlike *Mycobacterium tuberculosis*, is not strongly acid-fast. Therefore, sections must be decolorized

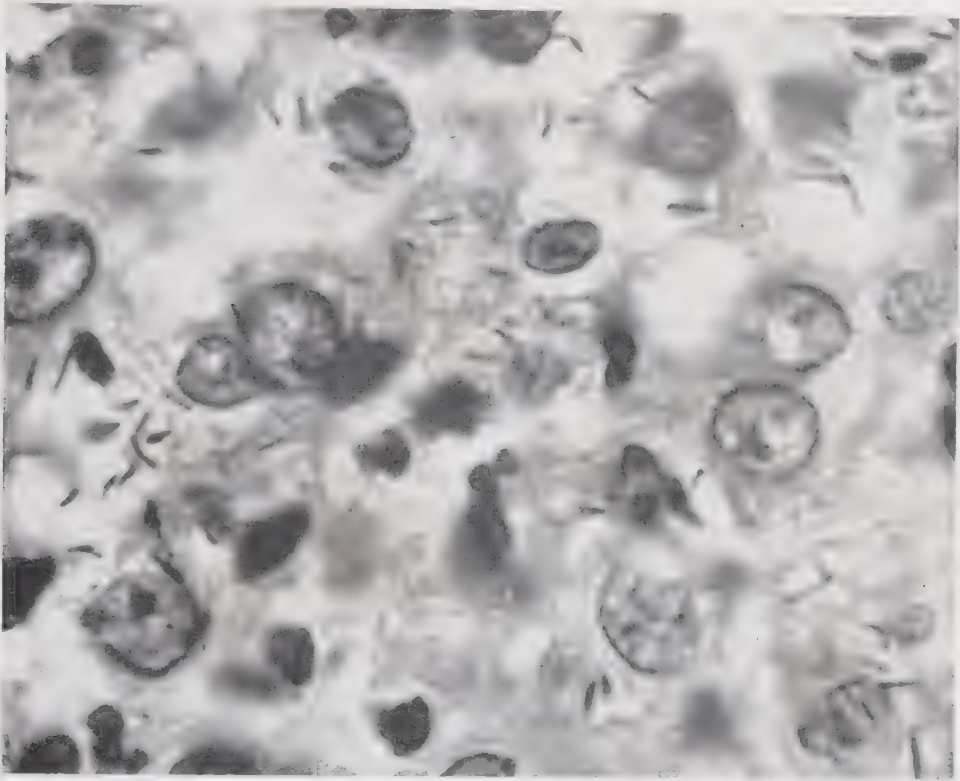


FIG. 93. Lepromatous leprosy, early stage. Ziehl-Neelsen stain. Numerous lepra bacilli are present. In the left center, two bundles of bacilli are shown. ($\times 800$)

lightly if leprosy is suspected (Allen). In older lesions, the histiocytes develop into fibroblasts and the number of lepra cells decreases. However, those present may be very large in size. In routine sections, they appear as round empty spaces so that they look like large lymphatics (Cowdry) (Fig. 94). On staining after Ziehl-Neelsen or Fite, they may or may not contain large globi of partially degenerated lepra bacilli.

Tuberculoid leprosy shows a tuberculoid infiltrate. Patients with tuberculoid leprosy have fairly good immunity against the lepra bacillus. This explains, in accordance with the Jadassohn-Lewandowsky law (see page 175), the scarcity or the absence of bacilli and the tuberculoid tissue response. Sections may show almost pure epitheli-

oid-cell tubercles so that differentiation from sarcoidosis may be difficult (Fig. 95). However, a thorough search usually will reveal invasion and destruction of nerves in the dermis or the subcutaneous tissue by epithelioid-cell tubercles, which never occurs in sarcoidosis. In some cases, the tubercles show a moderate admixture of lymphocytes and contain giant cells. However, caseation necrosis does not occur in the skin. *Lepra* bacilli may be absent in the lesions of tu-

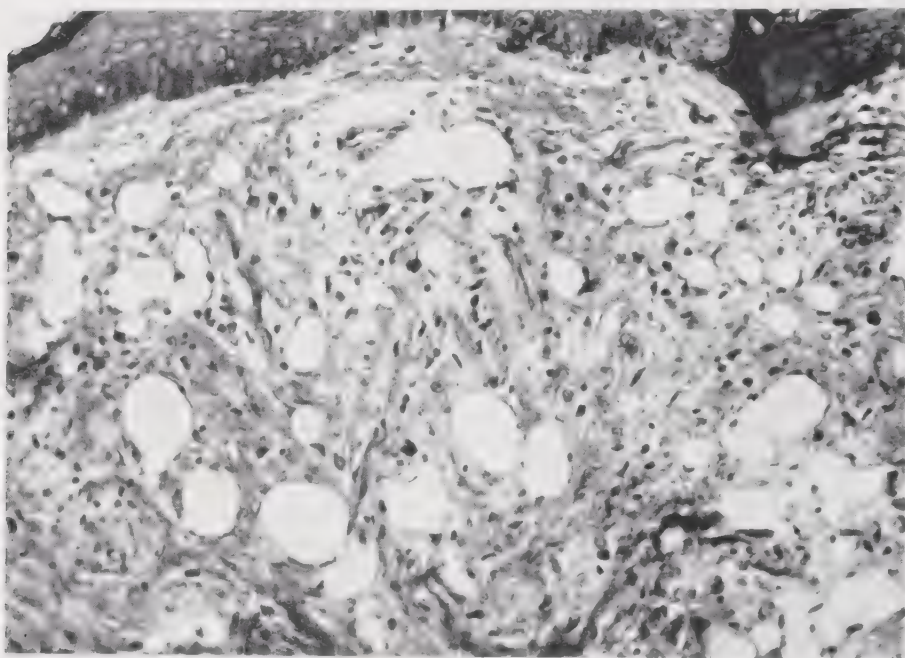


FIG. 94. Lepromatous leprosy, late stage. High magnification. There is some fibrosis. The lepra cells are very large in size and appear as round empty spaces. ($\times 200$)

berculoid leprosy, but not infrequently they are found in small numbers after prolonged search (Arnold, 1945).

Indeterminate leprosy shows only lymphocytic infiltration around the vessels and the nerves of the dermis. *Lepra* bacilli are found only with difficulty (Canizares).

NEURAL LESIONS. Lesions in the large peripheral nerves occur in almost every case of leprosy, regardless of type. In all three types, the histologic appearance of the neural lesions corresponds to that of the cutaneous lesions (Pardo-Castello, Tiant and Piñeyro). The nerve lesions of lepromatous leprosy show large vacuolated Virchow cells and numerous lepra bacilli. In tuberculoid leprosy, one observes in the nerves an extensive infiltrate of epithelioid-cell tubercles containing few or no bacilli. However, in contrast with the cutaneous lesions, caseation necrosis is common. In occasional instances, mas-

sive caseation of the tuberculoid lesions with complete destruction of nerve tissue occurs ("colliquative neuritis").



FIG. 95. Tuberculoid leprosy. Low magnification. The infiltrate consists of epithelioid-cell tubercles, showing a slight admixture of lymphocytes, particularly at their margins. Thus, the histologic picture is very much like that of sarcoidosis. ($\times 100$)

DIPHThERIA OF THE SKIN

The clinical picture of diphtheria of the skin is varied. Most commonly encountered are one or several punched-out ulcers covered with a pseudomembrane the removal of which is difficult and followed by profuse bleeding. Next in frequency are moist, crusted eczematous lesions which occur particularly in the retro-auricular region. Other types of lesions occasionally observed include impetiginous, vesicular and bullous lesions (Reiss).

Histopathology. The histologic picture of all forms of diphtheria is nonspecific. The ulcerative lesions show destruction of the epidermis and of the upper dermis within the region of the ulcer. At the margin of the ulcer, the epidermis is acanthotic. The dermis beneath the ulcer shows evidence of acute inflammation. The floor of the ulcer is covered with a layer composed of necrotic cells, fibrin and numerous neutrophils. In some instances, numerous Klebs-Loeffler bacilli can be seen in this necrotic layer (Allen). These bacilli have bipolar bodies and tend to lie in palisade-like arrangement. The finding of such bacilli is suggestive of diphtheria. However, since diphtheria bacilli cannot safely be differentiated from pseudodiphtheria bacilli in stained sections, smears and cultures are necessary for the establishment of the diagnosis.

The eczematous lesions may show the histologic picture of either an acute, a subacute or a chronic dermatitis. The histologic changes thus are identical with those observed in an ordinary bacterial dermatitis (Robert).

ANTHRAX

Anthrax, caused by *Bacillus anthracis*, is characterized by a carbuncle-like lesion located usually on an exposed portion of the skin. The lesion starts as a papule, enlarges, ulcerates and then becomes covered with a black eschar. Frequently, a ring of vesicles is present at the margin of the eschar. Marked erythema and edema surround the lesion. Suppuration does not occur. Pain is characteristically slight or absent. Often there is regional lymphadenopathy, which may be painful.

Histopathology. At the site of the ulcer, the epidermis is destroyed and the ulcerated surface is covered with necrotic tissue. The adjoining epidermis shows spongiosis and occasionally intra-epidermal vesicle formation and is invaded by neutrophils. There is marked edema of the dermis, separating the bundles of collagen and loosening their fibrils. Numerous erythrocytes and neutrophils are present throughout the dermis and the subcutaneous tissue. However, abscess formation is absent. Only few histiocytes can be observed. The blood vessels are dilated and their walls show diffuse degenerative changes.

Anthrax bacilli are present in large numbers and can be recognized in sections stained with routine stains but are visualized best in sections stained with Gram's stain. The anthrax bacillus is a large, rod-shaped, square-ended, Gram-positive bacillus, from 6 to 10 microns long and from 1 to 2 microns thick. In the tissue, it is usually surrounded by a well-defined capsule. Anthrax bacilli are found in countless numbers in the necrotic tissue at the surface of the ulcer. The dermis also contains numerous bacilli, while the subcutaneous

tissue usually contains only a few. It is worth noting that phagocytosis of the bacilli by either neutrophils or histiocytes is absent (Lebo-wich, McKillip and Conboy).

TULAREMIA

Tularemia, an infectious disease caused by *Bacterium tularensis*, occurs in four types: the ulceroglandular, the oculoglandular, the glandular and the typhoid types. Specific cutaneous lesions occur only in the ulceroglandular type. They are of two varieties: ulcers and nodes. One or several ulcers occur as primary lesions at the site of infection; they tend to have a punched-out appearance. Cutaneous or subcutaneous nodes form in the small lymph nodes located along the lymph vessels draining the primary lesion; they are hard and tender at first but may proceed to suppuration.

Histopathology. The primary ulcer shows a nonspecific granulation tissue into which are embedded granulomas composed of three zones: (1) a central zone of necrosis, consisting of finely granular eosinophilic material, nuclear fragments and a few erythrocytes; (2) an intermediate zone, composed of epithelioid cells with a few Langhans giant cells and lymphocytes and (3) an outer zone, consisting largely of lymphocytes but containing also some histiocytes, plasma cells and extravasated erythrocytes. Vascular changes in the outer zone and in the surrounding granulation tissue are conspicuous; they consist of proliferation of the endothelial cells and infiltration of the vascular walls by inflammatory cells (Schuermann and Reich). Older lesions may show epithelioid-cell tubercles with only a slight inflammatory reaction and thus may have a sarcoid-like appearance. *Bacterium tularensis*, although present, does not stain in the sections.

The cutaneous "lymphatic" nodes show, like the primary ulcer of tularemia, scattered granulomas in which three zones can be recognized.

Differential Diagnosis. The histologic picture differs from that of tuberculosis by the distinct arrangement in three zones which is rarely seen so clearly in tuberculosis, by the presence of vascular changes and by the presence of erythrocytes in the central, necrotic zone and the outer, lymphocytic zone (Reich). Differentiation from sporotrichosis (see page 230) and lymphogranuloma venereum (see page 252), however, may be impossible.

CHANCROID

Chancroid, caused by the streptobacillus of Ducrey (*Hemophilus ducreyi*), is a venereal disease causing one or several ulcers, chiefly

in the genital region. The ulcers show little if any induration and tend to have an undermined border. Regional lymphadenitis is common and usually terminates in abscess formation (bubo).

Histopathology. The chancroidal ulcer presents a granulomatous reaction which is sufficiently distinct to permit a diagnosis of chancroid in many instances (Heyman, Beeson and Sheldon). The lesion consists of three zones (Sheldon and Heyman) and shows characteristic vascular changes (Pund, Greenblatt and Huie). The surface zone or base of the ulcer is rather narrow and is made up of polymorphonuclear leukocytes, fibrin, red blood cells and necrotic tissue. Below this is a fairly wide zone of edematous tissue composed mainly of endothelial cells in varying stages of proliferation. Newly formed blood vessels are numerous. There is marked endothelial proliferation within the vessels, frequently blocking their lumina and leading to thrombosis. In addition, there is degeneration of the walls of vessels. The third zone is composed of a dense infiltration of plasma cells and lymphocytes.

Demonstration of Ducrey bacilli in the tissue by staining with Giemsa's stain, Gram's stain or with polychrome methylene blue is only rarely possible. They are most apt to be found as Gram-negative coccobacilli between the cells of the surface zone (Sheldon and Heyman).

GRANULOMA INGUINALE

Granuloma inguinale is a venereal disease caused by *Donovania granulomatis*, which is found in the lesions in the form of intracytoplasmic inclusion bodies, called Donovan bodies. The taxonomic position of *Donovania granulomatis* is as yet undecided but it is most likely a bacterium and not a virus. It grows well on the chorioallantoic membrane of chick embryos.

The lesions occur predominantly in the genital region and consist of sharply demarcated granulomatous areas which have a livid hue and bleed easily. The border is elevated and often shows a serpiginous outline. The lesions spread very slowly by peripheral extension and may attain large size. After years, the lesions heal with a thick, fibrous, contracted scar. In occasional instances, squamous-cell carcinoma supervenes (Beerman and Sonck; Alexander and Shields).

Histopathology. The epidermis may be thinned but more often shows acanthosis, which may reach the proportions of pseudo-epitheliomatous hyperplasia (Beerman and Sonck). A granulomatous infiltrate is present in the dermis, composed predominantly of histiocytes and plasma cells. Scattered throughout the otherwise mononuclear infiltrate one finds small abscesses composed of poly-

morphonuclear leukocytes (Allen). The number of lymphocytes is conspicuously small.

Intracytoplasmic inclusion bodies, called Donovan bodies, are present within a variable number of histiocytes. The parasitized histiocytes, or macrophages, possess abundant cytoplasm and may measure 20 microns and more in diameter. Their cytoplasm has a cystic appearance. Within the cystic compartments of the cytoplasm,

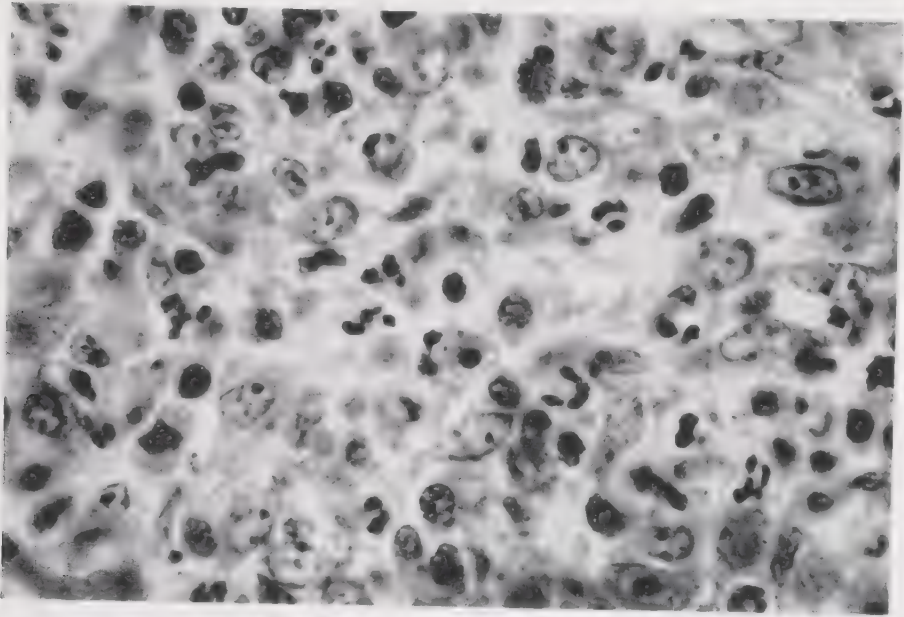


FIG. 96. *Granuloma inguinale*. The granulation tissue is composed predominantly of histiocytes and plasma cells. There is a diffuse sprinkling of polymorphonuclear leukocytes. Several of the histiocytes contain Donovan bodies within their cytoplasm. ($\times 400$)

one sees groups of small, round or oval, encapsulated bodies, measuring 1 to 2 microns in diameter (Fig. 96). In the cross-sections of large histiocytes, several dozen of such bodies may be observed. The Donovan bodies are recognizable in stains with hematoxylin and eosin, but are seen best in sections stained with Giemsa's stain. In such sections, they appear bright red (Alexander and Schoch). When a silver stain is used, the Donovan bodies appear black and have the shape of a closed safety pin because of their elongated ovoid shape and intense bipolar staining reaction (Torpin, Greenblatt and Pund). The capsule surrounding the Donovan bodies does not stain. In addition to their intracellular location, a few Donovan bodies may be found extracellularly, singly or in small groups.

Since the diagnosis of granuloma inguinale rests upon the demonstration of the Donovan bodies, it may be pointed out that it is often

easier to find them in tissue scrapings or tissue imprints stained with Giemsa's or Wright's stain than in fixed tissue sections.

Differential Diagnosis. The parasitism of histiocytes is strikingly similar to that observed in rhinoscleroma, histoplasmosis and leishmaniasis. However, the small size of the Donovan bodies and the presence of small abscesses in the infiltrate usually make a differentiation from these diseases possible. (See Table 5, page 237.)

A difficult problem may be posed by the marked epidermal proliferation present occasionally in granuloma inguinale (Beerman and Sonck). Several biopsies may be necessary to decide whether it represents merely pseudo-epitheliomatous hyperplasia (see page 334) or squamous-cell carcinoma which occasionally supervenes in granuloma inguinale.

RHINOSCLEROMA

Rhinoscleroma is a chronic infectious disease in which the nose, the lip and the upper respiratory tract are infiltrated with hard plaques and masses.

Histopathology. The granulomatous infiltrate is strikingly rich in plasma cells and contains two peculiar types of cells, the Mikulicz cell and the Russell bodies. Because of their presence, the histologic picture of rhinoscleroma is diagnostic.

The Mikulicz cell is a very large, round histiocyte measuring up to 100, occasionally even 200, microns in diameter. It has a pale, reticulated, ill-defined cytoplasm and an eccentric nucleus. If a bacterial stain, such as Giemsa's stain, is used, one finds within the cytoplasm of many Mikulicz cells, as well as in their vicinity, many bacilli, called *Klebsiella rhinoscleromatis* or Frisch bacilli (Fig. 97). They are short, Gram-negative rods, measuring 2 by 5 microns in length, and are surrounded by a narrow gelatinous capsule (called gloea). It is not certain that the disease is caused by this organism.

The Russell bodies are elliptic formations, measuring from 20 to 40 microns in diameter. Thus, they are smaller than a Mikulicz cell but still twice as large as a normal plasma cell. They have a homogeneous, brilliant red, light-refractile cytoplasm and no nucleus (Fig. 98). They form within plasma cells as a result of their degeneration and finally are expelled (see page 37).

The amount of cellular infiltration varies with the age of the lesion. Early lesions show considerable infiltration by numerous plasma cells and lymphocytes with occasional histiocytes and eosinophils; many Russell bodies are present but only few Mikulicz cells. Gradually, the number of Mikulicz cells increases to such extent that they predominate the histologic picture, giving the section a

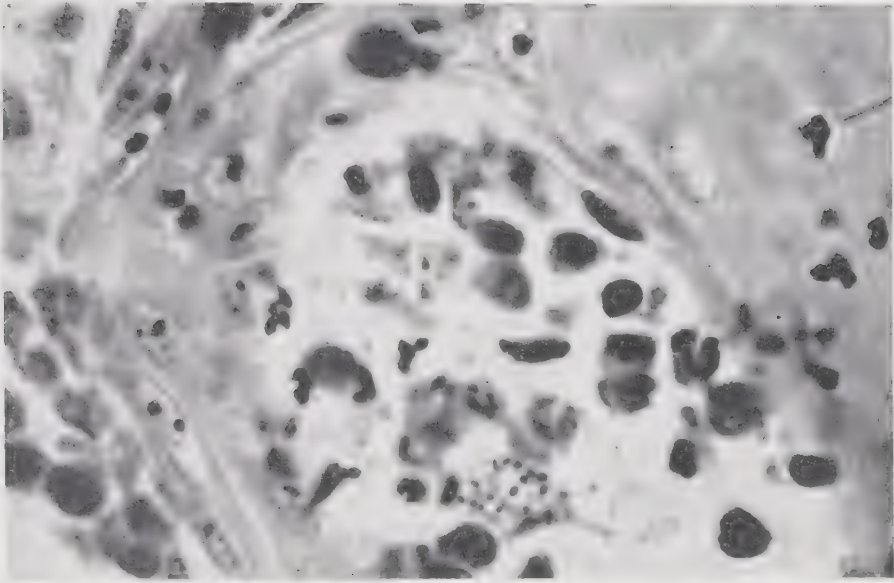


FIG. 97. **Rhinoscleroma.** Giemsa stain. There are several Mikulicz cells, the cytoplasm of which is pale, reticulated and ill-defined. One Mikulicz cell contains in its cytoplasm many Frisch bacilli, which appear here as small, round, deeply staining bodies. ($\times 900$)

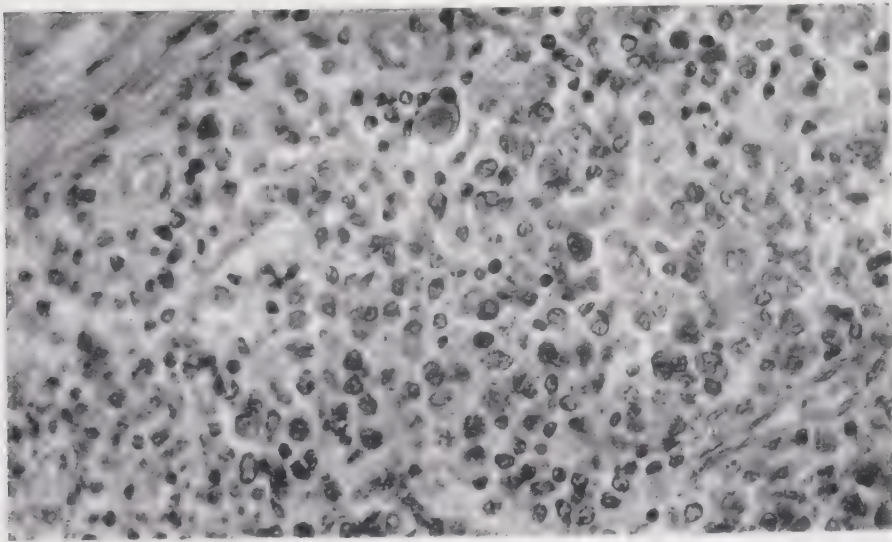


FIG. 98. **Rhinoscleroma.** The infiltrate contains many plasma cells and one Russell body. The Russell body is larger than the other cells in the infiltrate. It has a homogeneous, brilliant red, refractile cytoplasm. ($\times 400$)

foamy, lacelike appearance. Finally, fibrosis replaces the Mikulicz cells (Kline and Brody).

Differential Diagnosis. Parasitized histiocytes are observed also in cutaneous leishmaniasis, histoplasmosis and granuloma inguinale. For their differentiation, see cutaneous leishmaniasis (page 235 and Table 5, page 237). Russell bodies are not found in these three diseases and, therefore, are of considerable diagnostic value. However, they are not specific for rhinoscleroma because they may occur in other diseases when an infiltrate rich in plasma cells is present—for instance, in syphilis, tuberculosis, squamous-cell carcinoma and mycosis fungoides.

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12

Spirochetal Diseases

SYPHILIS

Acquired syphilis may be divided into three stages: primary, secondary and tertiary. Primary and secondary syphilis comprise the early phase and tertiary syphilis the late phase of the infection. During the early phase, the causative organism, *Treponema pallidum* (*Spirochaeta pallida*), often can be demonstrated in the cutaneous lesions by dark-field examination. In the late phase, no spirochetes can be demonstrated in the cutaneous lesions.

Primary syphilis is characterized by the syphilitic or hard chancre, which is usually a single lesion but may be multiple. The typical, or Hunterian, chancre is represented by a brownish red, indurated, round papule or plaque with an eroded surface. Occasionally, the chancre shows ulceration. The regional lymph nodes are enlarged.

Secondary syphilis is characterized by a more or less generalized eruption, which is composed usually of macules or papules having a brownish red color. In the anogenital region, the papules may become large, verrucous and moist; they are then called condylomata lata. (They must be differentiated from condylomata acuminata, a variety of verruca; see page 251.) In some instances, the cutaneous eruption, due to the presence of scaling, resembles psoriasis (psoriasiform syphilid). Occasionally, pustules develop and are followed by heavy crusting (rupial syphilid). Ulceration of lesions in secondary syphilis is very rare and occurs only in severe cases. Alopecia syphilitica is characterized by numerous small patches of partial, "moth-eaten" alopecia.

Tertiary syphilis often shows only a single lesion, but occasionally several lesions. A superficial, nodular type and a deep, gummatous type of tertiary syphilis occur. Lesions of the nodular type show an active, serpiginous border composed of nodules and a smooth, atrophic center. Lesions of the gummatous type begin as a soft cutaneous or subcutaneous swelling, which breaks down to form one or several ulcers having a punched-out appearance. In rare instances, juxta-articular nodes occur in tertiary syphilis. They are painless, slowly growing, subcutaneous, fibrous nodules, often symmetrically situated

in the vicinity of joints. The elbows and the knees are the sites of predilection.

Congenital, or prenatal, syphilis shows the same cutaneous manifestations as acquired secondary and tertiary syphilis with the following exceptions: first, occasionally bullous lesions occur, especially on the palms and the soles, as a manifestation of secondary syphilis in infants; and second, juxta-articular nodes do not occur.

Histopathology. The fundamental pathologic changes in syphilis are: (1) a predominantly perivascular infiltrate composed of lymphocytes and many plasma cells, and (2) endarteritis and endophlebitis. In tertiary syphilis, one usually finds, in addition, a tuberculoid infiltrate and caseation necrosis.

PRIMARY SYPHILIS. In the typical primary lesion, the epidermis shows, at the margin of the lesion, acanthosis. Toward the center, the epidermis gradually becomes thinner until, in the central portion, it is entirely absent (Fig. 99). An infiltrate composed of lymphocytes and many plasma cells is present in the dermis. It is compact in the center, while at the margin it consists of individual perivascular islands. Both blood and lymph vessels show changes. The capillaries and the lymphatics are increased in number and show considerable proliferation of their endothelial cells (Fig. 100). The larger blood vessels show proliferation of all their coats and invasion of their walls by the cellular infiltrate. Obliteration and thrombosis of the lumina of some of the vessels is common and results in small foci of necrosis. Occasionally, the lumina of so many vessels are occluded that massive necrosis results. In such cases, the primary lesion presents itself as an ulcer instead of an erosion.

On staining with Levaditi's stain, spirochetes usually can be found, often in large number. They are found throughout the tissue, but especially in and around the walls of capillaries and lymphatics.

Histologic examination of the regional lymph nodes in primary syphilis may reveal only a nonspecific inflammation; not infrequently, however, small foci of tuberculoid reaction are encountered in addition (Michelson).

SECONDARY SYPHILIS. In secondary syphilis, the number of spirochetes seen in sections stained with Levaditi's stain varies with the type of lesion. In the macular lesions of early secondary syphilis, spirochetes cannot be found, as a rule. In papular lesions, they are seen occasionally. In condylomata lata, they are almost always present in sufficient numbers to be found without difficulty. They occur not only in the dermis but also between epidermal cells.

The *macular lesions* of early secondary syphilis usually do not show a diagnostic histologic picture. The superficial capillaries show swell-

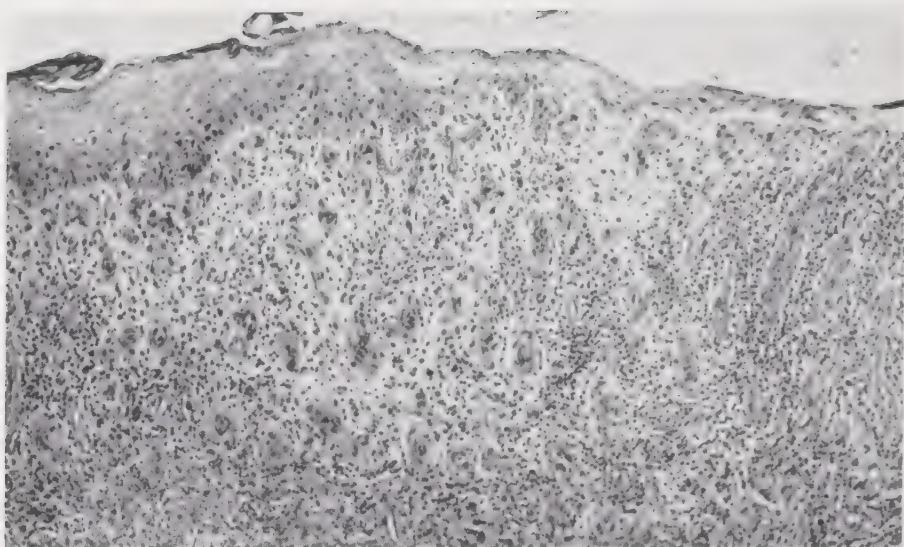


FIG. 99. Primary syphilis. Low magnification. The margin of an erosion is shown. The epidermis gradually becomes thinner as it approaches the erosion. ($\times 100$)

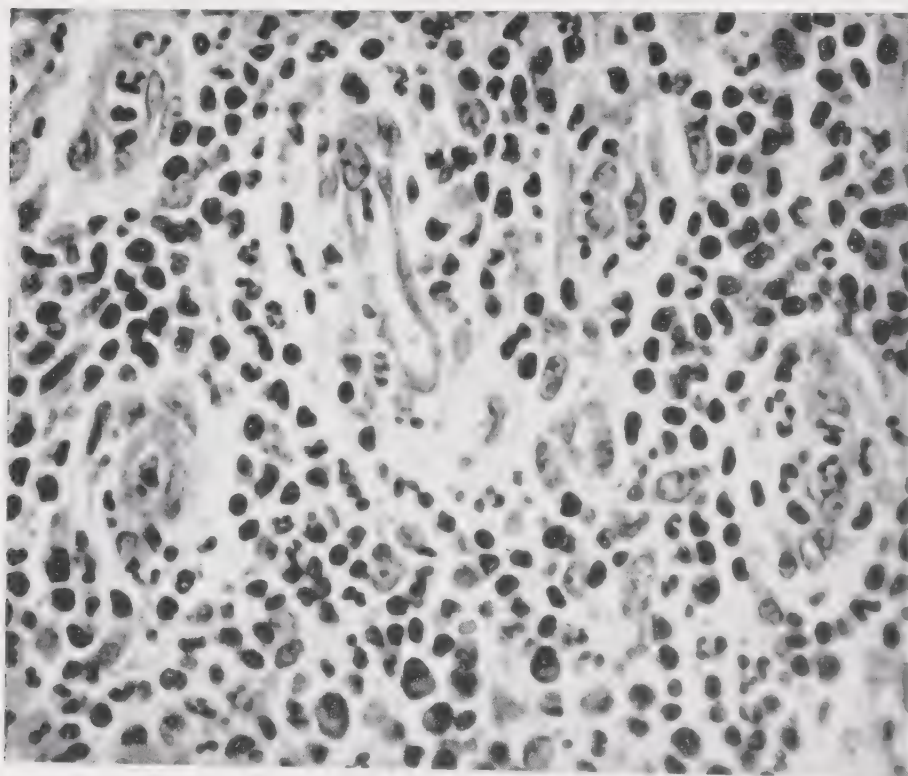


FIG. 100. Primary syphilis. High magnification of Figure 99. The capillaries are greatly increased in number and show marked proliferation of their endothelial cells. Many plasma cells are present in the dense infiltrate. ($\times 400$)

ing of their endothelium and are surrounded by a slight infiltrate of lymphocytes and plasma cells. However, the number of plasma cells is not sufficiently large to be of diagnostic value.

Papular lesions, as a rule, have a diagnostic appearance. Not only the superficial but also the deeper vessels of the dermis are involved. They show marked endothelial swelling and are surrounded by a pronounced infiltrate (Fig. 101). Because of its perivascular "coat-sleeve-like" arrangement, the infiltrate has a patchy distribution. The patchy pattern stands out very clearly in the lower dermis. In the upper dermis, in addition to the patchy infiltrate, there may be a diffuse scattering of cells. Usually, a significantly high number of plasma cells is present in the infiltrate (Fig. 102). In the differential diagnosis, simple chronic dermatitis and the exudative discoid and lichenoid chronic dermatosis of Sulzberger and Garbe have to be excluded. The latter, in particular, may suggest secondary syphilis because of the patchy distribution of its infiltrate and the presence of many plasma cells; but neither chronic dermatitis nor exudative discoid and lichenoid chronic dermatosis shows the marked endothelial swelling of the vessels and the extension of the patchy infiltrate into the lower dermis.

Condylomata lata show the same changes in the dermis as the papular lesions. In addition, the epidermis shows considerable acanthosis, with broadening and elongation of the rete ridges, intracellular and intercellular edema of the rete cells and migration of polymorphonuclear leukocytes through the epidermis.

Psoriasisiform secondary syphilis may show epidermal changes similar to those of psoriasis, but the dermal infiltrate is that of secondary syphilis and not of psoriasis.

Rupial secondary syphilis shows a pronounced, acute inflammatory infiltrate in the upper dermis, permeation of the epidermis by neutrophils and subcorneal pustules. The diagnosis of syphilis usually can be made because the lower dermis shows the characteristic infiltrate of secondary syphilis.

Ulcerative lesions are rare in secondary syphilis. They occur when the larger vessels at the border of the dermis and the subcutaneous tissue become completely occluded by syphilitic endarteritis and endophlebitis (Wile, Wieder and Warthin).

In *syphilitic alopecia*, one may find a perifollicular infiltrate composed of lymphocytes, many plasma cells and occasionally a few giant cells (symptomatic alopecia). In many instances, however, no infiltrate is found (essential alopecia). Wile and Belote believe that, in the latter type of alopecia syphilitica, the loss of hair is not through local action of the spirochetes but through the action of spirochetes

on endocrine glands or on the autonomic nervous system. Meningeal syphilis is common with that type.

It is not always possible to assign, on the basis of histologic examination, cutaneous lesions of syphilis to either secondary or tertiary syphilis. Not infrequently, one finds in lesions which clinically are to be classified as late secondary syphilis an admixture of epithelioid and giant cells. On the other hand, lesions of early tertiary syphilis

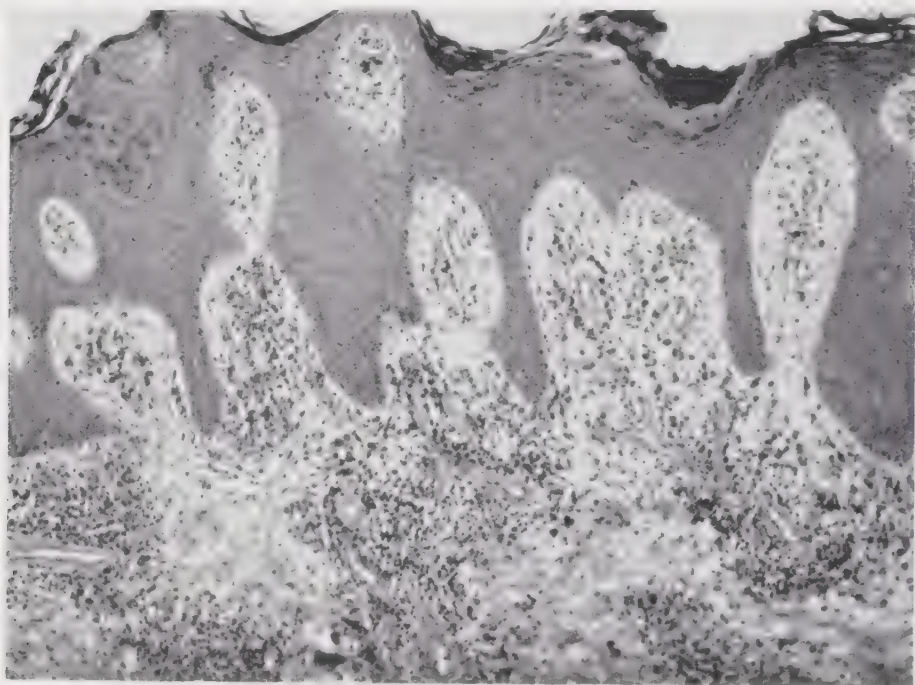


FIG. 101. Secondary syphilis. Low magnification. The vessels throughout the dermis show endothelial proliferation. The cellular infiltrate is located around the vessels in "coat-sleeve" arrangement. ($\times 100$)

may show the histologic infiltrate of secondary syphilis without any epithelioid and giant-cell reaction.

TERTIARY SYPHILIS. In tertiary syphilis, one observes a granulation tissue composed of lymphocytes, plasma cells, histiocytes, fibroblasts and varying numbers of epithelioid and giant cells. Usually, but not always, the number of plasma cells is prominent. The infiltrate is massive in the center but tends to have a perivascular arrangement at the periphery. Vascular changes are prominent, particularly in the larger vessels. They show proliferation of their walls leading to narrowing of their lumina, and invasion of their walls by the inflammatory infiltrate. Caseation necrosis is frequent. It is probable that caseation necrosis is not due to the vascular changes, because often the vascular changes are just as severe in areas without caseation as in areas with caseation. It seems more likely that caseation represents

an allergic phenomenon caused by alteration in the reactivity of the tissue (Boyd). In the healing stage, lesions of tertiary syphilis show numerous fibroblasts. The process ends in fibrosis. Tertiary syphilis occurs in the skin in two forms: nodular and gummatous.

In *nodular tertiary syphilis*, the granulomatous process is limited to the dermis. The number of epithelioid and giant cells is small.

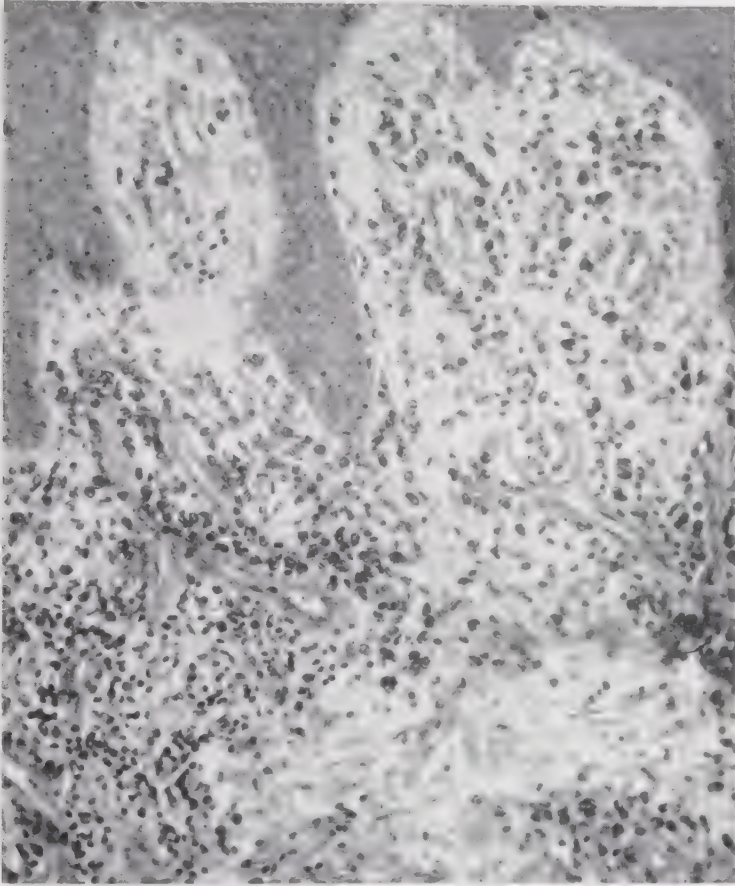


FIG. 102. Secondary syphilis. High magnification of Figure 101. The perivascular infiltrate contains many plasma cells. ($\times 200$)

as a rule. Occasionally, however, these cells are fairly numerous in the center of the lesion. They tend to lie without arrangement into real tubercles, and giant cells of the foreign-body type are more common than those of the Langhans type (Fig. 103). Caseation necrosis is usually not extensive and may be absent. If extensive, ulceration results.

In *gummatous tertiary syphilis*, the granulomatous process is more widespread than in the nodular form and involves the subcutaneous tissue in addition to the dermis. Epithelioid and giant cells are numerous and massive caseation necrosis occurs in the center of the

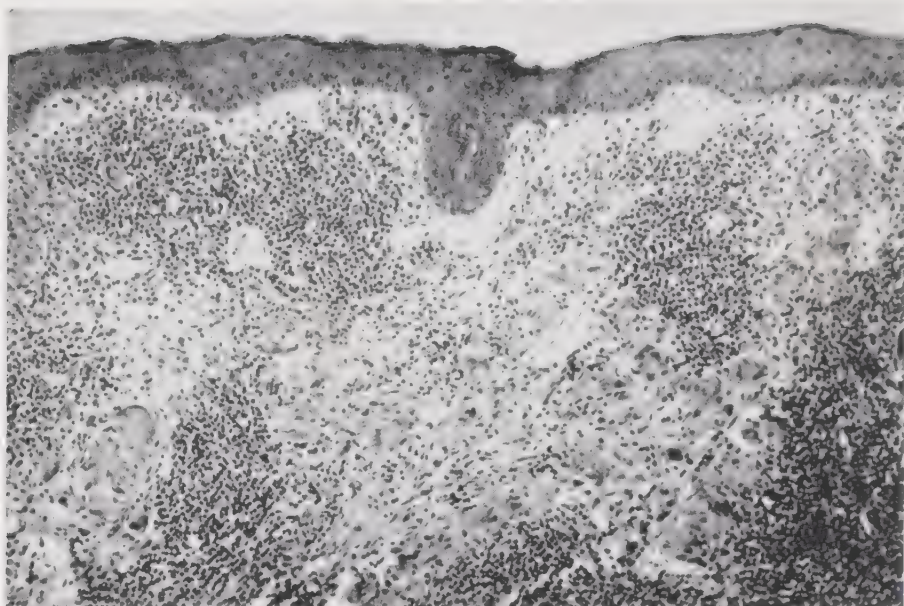


FIG. 103. Tertiary syphilis, nodular type. In the center of the field, a large island of epithelioid and giant cells is located. Most giant cells are of the foreign-body type rather than of the Langhans type. The infiltrate at the margins contains many plasma cells. ($\times 100$)

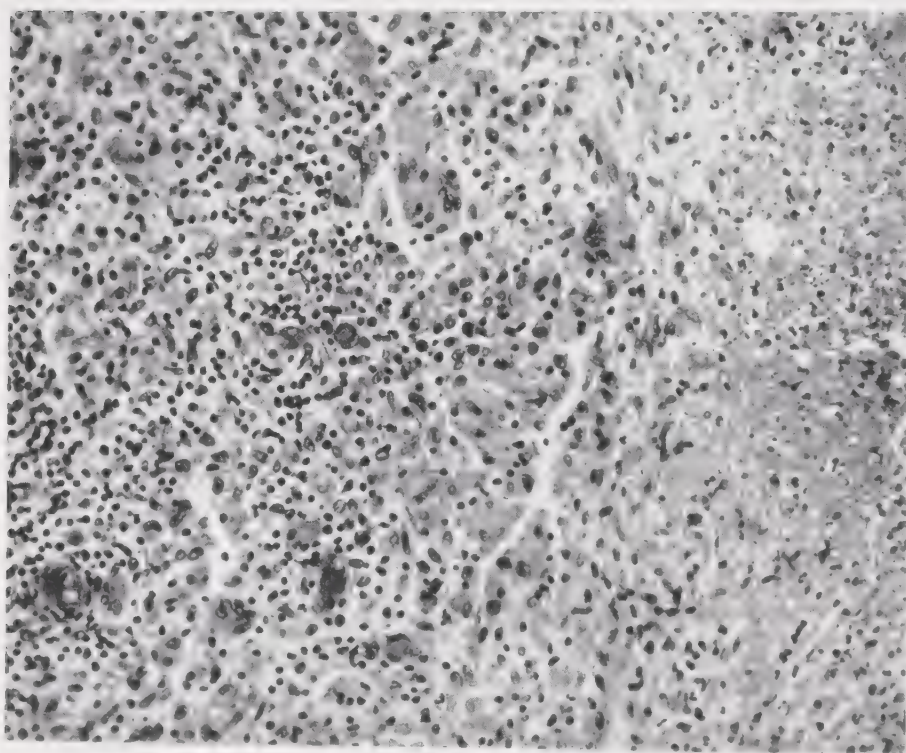


FIG. 104. Tertiary syphilis, gumma. On the left side of the field, the infiltrate consists of lymphocytes and many plasma cells. In the center, numerous epithelioid and giant cells are present. Most giant cells are of the foreign-body type. On the right side, one sees part of the large area of caseation necrosis which forms the center of the gumma. ($\times 200$)

lesion (Fig. 104). The epithelioid and the giant cells are located mainly in the vicinity of the areas of caseation. Because of the deep extension of the process, not only the vessels of the dermis, as in nodular tertiary syphilis, but also the large vessels of the subcutaneous layer are markedly involved.

Differentiation of tertiary syphilis from tuberculosis may be difficult. In the absence of caseation, the nodular type may resemble lupus vulgaris and the gummatous type may suggest scrofuloderma or erythema induratum. The latter, in particular, may be difficult to exclude because it shows obliterative vascular changes similar to those of tertiary syphilis. But, aside from erythema induratum, vascular changes provide the most important point of differentiation between syphilis and tuberculosis. In addition, the prevalence of plasma cells and the presence of giant cells of the foreign-body type rather than of the Langhans type favor a diagnosis of syphilis.

In *juxta-articular nodes*, the histologic picture varies with the age of the lesion. Early lesions are fairly cellular (Tuta and Coombs) and present, embedded in a dense fibrous tissue, granulomatous areas composed of epithelioid cells, lymphocytes and plasma cells, with an occasional Langhans type of giant cell. The blood vessels have thickened walls and are surrounded by dense accumulations of plasma cells. Well-developed lesions show an arrangement in three zones (Kalz and Newton), namely, an outer granulomatous zone in which the histologic picture is the same as just described for early lesions; an intermediate zone showing dense fibrous tissue with only few cells; and an inner zone showing hyalinized fibrous bands ramifying to form partitions for cystic spaces. The cystic spaces contain amorphous material and, occasionally, cholesterol clefts. In the late stage, the lesion is composed entirely of hyalinized fibrous tissue and shows no cellular infiltrate (Freeman). Occasionally, it is possible to demonstrate in early nodes the presence of spirochetes (Allen). Jessner as well as Hu, Liu, Chen and Frazier have succeeded in producing syphilis in rabbits by inoculating them with portions of *juxta-articular nodes*.

CONGENITAL SYPHILIS. The histologic changes in the cutaneous lesions of early congenital syphilis are similar to those seen in acquired secondary syphilis, except for the bullous lesions of the palms and the soles. The latter may show no plasma cells in the dermal infiltrate but numerous polymorphonuclear leukocytes and a few lymphocytes. Obliterative vascular changes are present, however (Fraser).

SYPHILIS OF INTERNAL ORGANS. It is not appropriate to discuss here in detail the histologic appearance of the lesions of syphilis in the

internal organs. However, it may be pointed out that late syphilis may cause two types of reactions in the internal organs: gumma and diffuse interstitial inflammation. The latter reaction is more common.

The gummata in internal organs show the same histologic changes as those observed in the skin.

Diffuse interstitial syphilitic inflammation manifests itself as accumulations of lymphocytes and plasma cells around the small vessels. Caseation is usually absent. As a result of the long-continued inflammation, there is gradual degeneration of the parenchymatous structures and their replacement by fibrous tissue (Boyd). This type of reaction produces, for instance, syphilitic hepatic cirrhosis. Syphilis of the aorta is also of the diffuse type. The process starts around the vasa vasorum of the adventitia. The inflammatory infiltrate then extends along the vasa vasorum into the media. In the media, one observes foci of inflammatory cells, miliary necrosis and extensive destruction of elastic tissue.

General paresis shows perivascular accumulations of lymphocytes and plasma cells in the meninges and in the cortex of the brain. In addition, there is extensive degeneration of the cortex. In contrast to general paresis, tabes does not show inflammatory changes. The essential lesion is degeneration of the posterior columns of the spinal cord.

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13

Fungus Diseases

DERMATOPHYTOSIS (TINEA)

The following are the most important fungi causing superficial fungus infections: *Microsporum canis* (*lanosum*), *Microsporum audouini*, *Trichophyton mentagrophytes* (*gypseum*), *Trichophyton rubrum* (*purpureum*), *Epidermophyton floccosum*, *Trichophyton* (*Achorion*) *schoenleini*, *Malassezia furfur* and *Nocardia* (*Actinomyces*) *minutissima*.

Clinically, nine types of superficial fungus infections can be recognized: (1) tinea capitis, (2) tinea barbae, (3) tinea corporis, (4) tinea cruris, (5) dermatophytosis of the feet and the hands, (6) onychomycosis, (7) favus, (8) tinea versicolor and (9) erythrasma.

Tinea capitis, which occurs almost exclusively in children, usually is caused either by *Microsporum canis* or by *Microsporum audouini*. The affected hairs tend to break off. *Microsporum canis* may evoke pronounced inflammation of the scalp, so-called kerion Celsi, while *Microsporum audouini* usually produces little inflammatory reaction.

Tinea barbae, rare in the United States, is usually caused by *Trichophyton mentagrophytes*. It is characterized by a boggy inflammatory infiltration in the bearded region of men.

Tinea corporis, if caused by *Microsporum canis*, manifests itself as multiple annular lesions with an active, often vesicular border and central clearing; if caused by *Trichophyton mentagrophytes*, one finds only one or at the most a few annular lesions showing little or no central clearing; if caused by *Trichophyton rubrum*, there are fairly sharply demarcated, sheetlike areas of erythema with slight scaling.

Tinea cruris, usually caused by *Epidermophyton floccosum*, produces areas of erythema and scaling with a slightly elevated, often vesicular border on the opposing surfaces of the skin between the scrotum and the thighs and in the perineal and the gluteal regions.

Dermatophytosis of the feet and the hands, usually caused by *Trichophyton mentagrophytes* and occasionally by *Epidermophyton floccosum*, is characterized by maceration between and underneath

the toes and an erythematous, scaling and vesicular eruption on the feet and the hands, especially the soles and the palms.

Onychomycosis, caused usually by *Trichophyton rubrum*, shows disintegration of the nail substance.

Favus, rare in this country, is caused by *Trichophyton (Achorion) schoenleini*. Most commonly it affects the scalp, where it produces inflammation with formation of perifollicular crusts, called scutula. Destruction of the hair ensues. Healing takes place with scarring.

Tinea versicolor, caused by *Malassezia furfur*, most commonly affects the upper trunk, where one finds areas of brownish discoloration. The surface of the discolored areas shows fine branny scaling.

Erythrasma, caused by *Nocardia minutissima*, consists of circumscribed, reddish brown, slightly scaling patches in the axillae and the groins.

Histopathology. For the demonstration of fungi in histologic sections, the periodic acid-Schiff stain of Hotchkiss-McManus is of very great value since it stains fungi deeply red while almost all other structures stain a very pale pink (Kligman and Mescon). It should always be used when the presence of fungi is suspected. The reason for the strongly positive reaction of fungi to the periodic acid-Schiff (PAS) stain is that the cell walls of fungi are composed of mixtures of cellulose and chitin which are rich in polysaccharides (Kligman, Mescon and DeLamater).

In histologic sections, fungi may present two structures: hyphae (or mycelia) and spores. Hyphae, which are nonreproductive, appear as threadlike structures; they may be septate or nonseptate. The spores which represent reproductive cells appear as round bodies.

TINEA OF THE GLABROUS SKIN. In tinea of the glabrous skin, fungi are present in small numbers with the exception of tinea versicolor in which the causative organism, *Malassezia furfur*, is always present in abundance. The fungi are found situated mainly in the upper two thirds of the stratum corneum. They may penetrate as far down as the upper layer of the stratum granulosum, but they do not occur between living cells. In tinea of the glabrous skin, except tinea versicolor, the fungi occur as short and long, segmented and occasionally granular hyphae extending parallel to the surface; spores are usually not observed (Peck). In tinea versicolor, one sees not only hyphae but also spores.

In the absence of fungi, no diagnostic picture is presented by fungus infections of the glabrous skin. In most instances, depending on the degree of reaction of the skin to the presence of fungi, one sees the histologic picture of either an acute, a subacute or a chronic dermatitis (see p. 68). Dermatophytosis of the hands and the feet

most frequently presents the histologic picture of a subacute dermatitis with intra-epidermal, "spongiotic" vesicles (Peck).

TINEA CAPITIS AND TINEA BARBAE. In tinea capitis and tinea barbae, fungi are present not only in the horny layer of the skin but also within and around the hair. Kligman, who recently has studied histologically the sequence of events in infections of human hair with *Microsporum canis* and *Microsporum audouinii* found that,

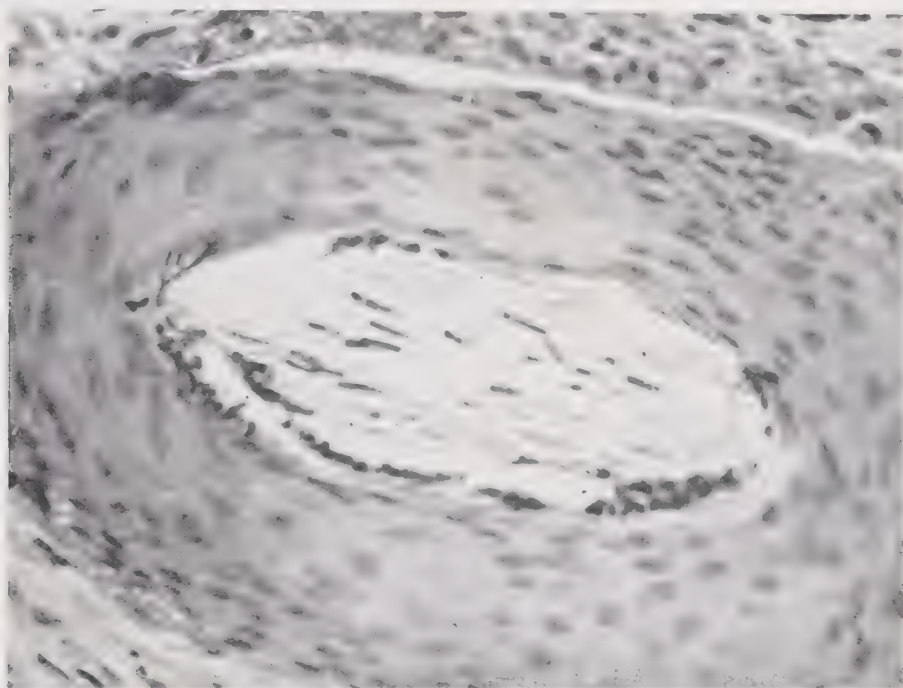


FIG. 105. Favus. Periodic acid-Schiff stain. The cross-section of a hair follicle is shown. The fungus, *Trichophyton schoenleinii*, is present, largely as mycelia, within and around the hair. ($\times 400$)

after infection of the scalp surface, hyphae grow downward into the follicle on the hair's surface a short distance and then penetrate into the hair. Inside the hair they form branches and grow downward but not farther than the exact limit of the zone of keratin synthesis. Thus, as in the surface epidermis, only fully keratinized structures are invaded. After the invasion of the hair, ectothrix spores are formed by segmentation of external branches of intrapilary hyphae. Within the hair, however, the hyphae form no spores. As the infection subsides, there is gradual reduction in the quantity of intrapilary hyphae and ectothrix spores.

Aside from the presence of fungi, the histologic picture in tinea capitis and tinea barbae may be merely one of subacute or chronic dermatitis. In kerion Celsi and tinea barbae, however, folliculitis

and perifolliculitis (see page 168) frequently are seen. At first, an intrafollicular abscess forms. The wall of the follicle may then rupture, whereafter the perifollicular tissue becomes the seat of an abscess. After discharge of the pus, the abscess cavity begins to fill in with granulation tissue. At that stage, epithelioid cells and foreign-body giant cells are frequently present, digesting remnants of the follicular epithelium (McCarthy). It may be pointed out that the histologic pictures of tinea barbae and folliculitis barbae (sycosis vulgaris) are essentially the same (see page 169).

FAVUS. The fungus is present in the horny layer of the skin, within and around the hairs (Fig. 105), and in the scutula. In some instances, the fungus invades the stratum malpighii and even the dermis (Ormsby and Montgomery). The scutula are composed at their periphery of well-preserved hyphae and spores, while in the center one finds granular debris and degenerated spores. The scutula rest upon an atrophic epidermis. The hair follicles underlying the scutula are destroyed. The dermis shows a mild to moderately severe inflammatory reaction.

MONILIASIS

Candida albicans, the cause of moniliasis, not only is a cutaneous pathogen but also may affect mucosal surfaces, such as the oral mucosa and the vagina. In rare instances, *Candida albicans* may infect the lungs or the meninges and cause death.

Clinically, cutaneous moniliasis usually is a superficial infection characterized by fairly sharply demarcated areas of erythema with or without pustulation. The intertriginous areas are predominantly affected. Paronychia is common. In rare instances, granulomatous and hyperkeratotic lesions form on the face and the scalp of children, so-called monilial granuloma; and, in adults, abscess formation and ulceration may occur.

The association of cutaneous and mucosal moniliasis with hypoadrenalism (Talbot, Butler and MacLachlan) and with hypoparathyroidism (Sutphin, Albright and McCune) is known to occur. Since this association is often familial, it is likely that both the endocrine deficiency and the susceptibility to monilial infection in these cases are due to some defect in the germ plasm.

Histopathology. Superficial cutaneous moniliasis presents a histologic picture like that found in subacute or chronic dermatitis. The fungus elements occur only in the stratum corneum. They consist of hyphae and spores, some of the latter in a budding stage.

Monilial granuloma shows hyperkeratosis, acanthosis and, in the dermis, a dense infiltrate of lymphocytes, plasma cells, neutrophils

TABLE 4.—HISTOLOGIC APPEARANCE OF THE TISSUE AND OF THE FUNGI IN FUNGUS DISEASES

DISEASE	HISTOLOGIC APPEARANCE OF TISSUE	AVERAGE SIZE OF FUNGUS (MICRONS)	APPEARANCE OF FUNGUS IN TISSUE
Moniliasis.....	When invasive: nonspecific granulation tissue with abscess formation	4	Hyphae and budding as well as nonbudding yeast cells (spores)
Blastomycosis.....	Epithelial hyperplasia; tuberculoid granulation tissue with formation of small abscesses	10	Thick-walled spores in giant cells and tissue. Budding forms
Torulosis.....	Chronic inflammatory infiltrate with extensive caseation	7	Spores with wide gelatinous capsule
Chromoblastomycosis.	Like blastomycosis	10	Thick-walled, dark brown spores, often in clusters. Some cells possess cross walls
Coccidioidomycosis	Granulomatous nodules: like blastomycosis except that caseation may occur. Subcutaneous abscesses: central caseation surrounded by tuberculoid granulation tissue	40	Thick-walled spores with granular cytoplasm. The larger spores contain endospores
Actinomycosis.....	Nonspecific granulation tissue with abscess formation	150	Large, irregularly lobulated granules with branching filaments and club formation at the periphery
Sporotrichosis.....	Primary lesion: nonspecific granulation tissue. Subcutaneous nodules: three zones: chronic suppurative, tuberculoid and syphiloid zone	(5)	Usually, no fungi are seen. Occasionally, asteroid forms of spores are present
Histoplasmosis.....	Chronic granuloma with foci of necrosis	3	Numerous spores surrounded by a clear halo lie in the cytoplasm of large histiocytes

and foreign-body giant cells. The infiltrate may extend into the subcutis. As a rule, *Candida albicans* is present only in the stratum corneum and not in the dermis (Hauser and Rothman).

In the rare instances of abscess formation and ulceration due to *Candida albicans*, hyphae as well as spores have been found in the dermis, especially in the abscesses and their vicinity. The spores measure about 4 microns in diameter, have a distinct capsule and

are Gram-positive. They often lie in clusters and budding forms are occasionally seen. The hyphae are slender rods and have a beaded or segmented appearance (Rockwood and Greenwood; Danbolt).

NORTH AMERICAN BLASTOMYCOSIS (GILCHRIST'S DISEASE)

North American blastomycosis, caused by *Blastomyces dermatitidis*, is characterized by granulomatous and suppurative lesions which may occur in any organ of the body but are found most commonly in the skin, the lungs and the bones. Two clinical forms can be differentiated, a primary cutaneous and a systemic form. In the benign primary cutaneous form, one observes either one or a few rather large lesions. In the fatal systemic form, the cutaneous lesions are numerous and usually small in size.

The cutaneous lesions consist in both forms of verrucous plaques showing an active border beset with a large number of minute abscesses. In the primary cutaneous form, the older lesions show central healing with atrophy. In the systemic form, the cutaneous lesions may undergo ulceration and, in addition, subcutaneous abscesses may occur.

Histopathology. Histologic examination shows acanthosis, papillomatosis and considerable downward proliferation of the epidermis. The downward proliferation may be marked enough to present the picture of pseudo-epitheliomatous hyperplasia. Intra-epidermal abscesses are often present. Occasionally, one finds Langhans giant cells completely enclosed by the proliferated epidermis (Fig. 106).

The dermis is infiltrated by a polymorphous granulation tissue. Polymorphonuclear leukocytes usually are present in large numbers and form small abscesses in the dermis. Langhans giant cells are scattered throughout the dermis. They usually lie alone and not within groups of epithelioid cells. Occasionally, one observes tuberculoid formations but never true tubercles.

The cells, or spores, of *Blastomyces dermatitidis* are fairly numerous in histologic sections. They are often found lying free in the tissue, particularly in the abscesses. They occur, however, in their largest number within the giant cells. One or several spores may lie within a giant cell (Fig. 107). When in this location, the spores are easily spotted, even at low magnification, in sections stained with routine stains. Being unstained, they resemble small, round holes punched out of the cytoplasm of the giant cells. On high magnification, the spores are seen to have a thick wall, which gives them a double-contoured appearance. They measure from 8 to 15 microns in diameter, on the average 10 microns. *Blastomyces* reproduce by



FIG. 106. North American blastomycosis. Low magnification. There is pseudo-epitheliomatous hyperplasia. Many giant cells of the Langhans type are present in the dermis as well as enclosed in the downward proliferations of the epidermis. ($\times 50$)

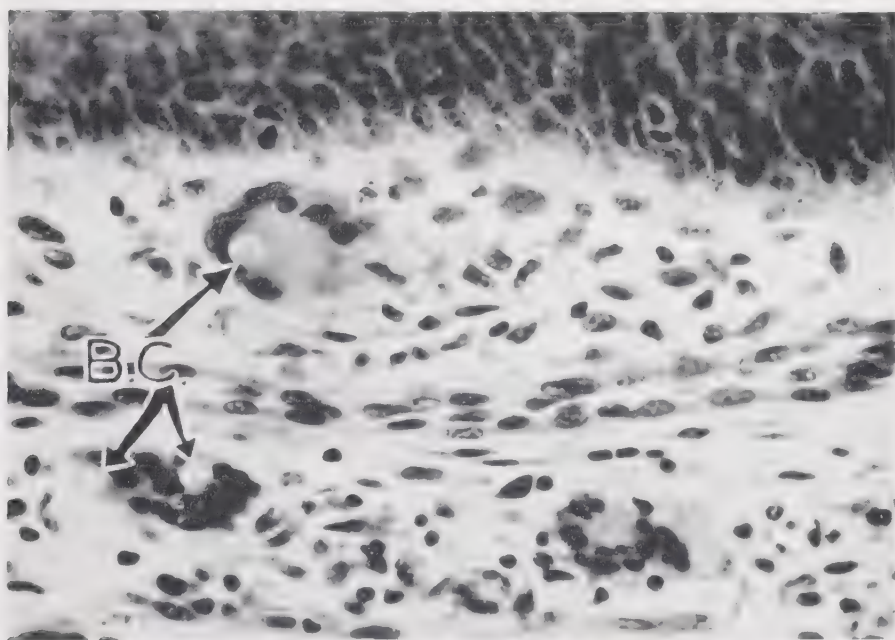


FIG. 107. North American blastomycosis. High magnification of Figure 106. Three blastomycetes cells (B.C.) are shown lying in the cytoplasm of giant cells. ($\times 400$)

budding, and occasionally budding forms are seen in sections. Like in most fungus infections, many more spores are seen in sections stained with the Hotchkiss-McManus stain than in routinely stained sections (see page 218).

The histologic appearance of the visceral lesions is analogous to that of the cutaneous lesions. The number of neutrophils is often great and numerous abscesses tend to be present (Littman, Wicker and Warren).

Differential Diagnosis. Tuberculosis verrucosa cutis, torulosis and chromoblastomycosis must be considered in the differential diagnosis. Tuberculosis verrucosa cutis shows no spores in the tissue. In addition, the number of neutrophils is much smaller and one usually finds true tubercles and areas of caseation necrosis. The distinctive features of torulosis and chromoblastomycosis are discussed under these respective headings (see below).

TORULOSIS (CRYPTOCOCCOSIS, EUROPEAN BLASTOMYCOSIS OF BUSSE AND BUSCHKE)

Torulosis, though very rare, occurs throughout the world. The disease, caused by *Cryptococcus neoformans* (*Torula histolytica*), usually is chronic and systemic and ends in death. The brain and the meninges are nearly always affected, resulting in meningo-encephalitis with presence of the organisms in the spinal fluid. The lungs also are commonly involved. Cutaneous lesions are present in about 10 per cent of the cases, and, in rare instances, lesions of the oral mucosa occur (Cawley). The cutaneous lesions may be the first clinical sign of the disease (Linell, Magnusson and Norden), and in some instances the disease may remain limited to the skin (Gandy). In that case, the course of the disease is benign and self-limited.

The occurrence of torulosis has been reported either as a silent or as an active infection in patients with various types of lymphoma, such as Hodgkin's disease (Geudel, Ende and Norman) and various types of leukemia (Cawley). A similar association with lymphoma occurs also in histoplasmosis (see page 231).

The cutaneous lesions are variable and may consist of papules, pustules, nodules, infiltrated plaques, ulcers or subcutaneous abscesses.

Histopathology. Histologic examination of the skin shows, in most instances, a chronic inflammatory infiltrate with or without giant cells. Occasionally, the inflammatory reaction is mild and extensive caseation is present in the dermis.

The causative fungus usually is present in abundance, either within

giant cells or lying free in the tissue. It consists of a spherical spore measuring from 5 to 10 microns in diameter which multiplies, like *Blastomyces dermatitidis*, by budding. It usually is surrounded by a wide gelatinous capsule which does not stain with hematoxylin and eosin but stains red with the periodic acid-Schiff reaction, and metachromatically purple with polychrome methylene blue (Linell, Magnusson and Norden). In some cases, however, the capsule is absent (Wile). The fungus then greatly resembles *Blastomyces dermatitidis* and easily can be confused with it, especially since both may occur in giant cells. On cultures, however, in contrast with *Blastomyces*, *Torula* forms no mycelia (Benham).

CHROMOBLASTOMYCOSIS

This disease is limited to the skin and is benign. It is caused by three closely related fungi which appear alike in the tissue: *Hormo-*

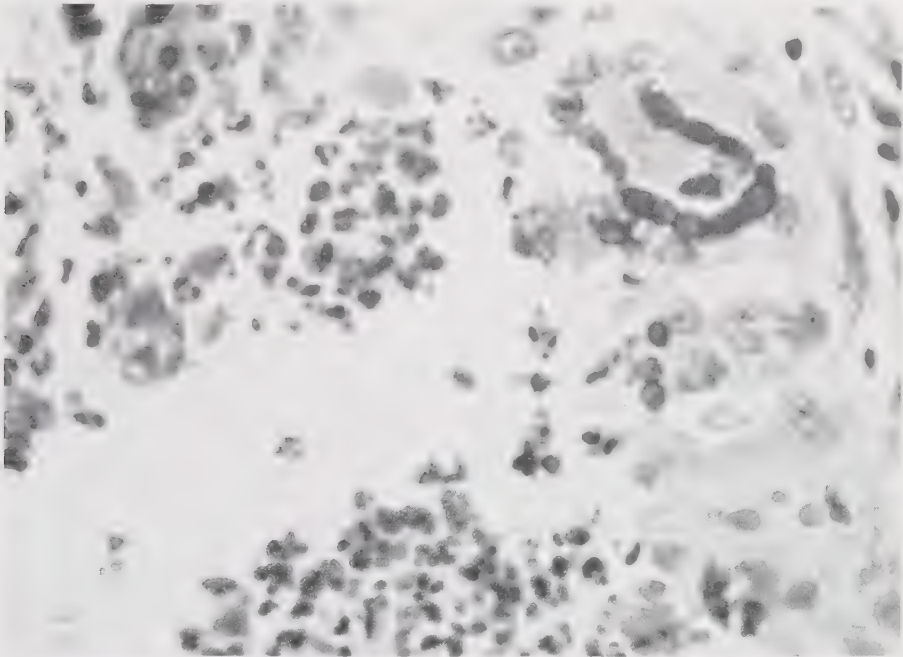


FIG. 108. Chromoblastomycosis. Periodic acid-Schiff stain. Epithelioid cells and Langhans giant cells form the wall of an abscess. Two long chains of fungus cells are located in the right upper corner. In addition, three fungus cells lie in the right center. ($\times 400$)

dendrum pedrosoi, *Phialophora verrucosa* and *Hormodendrum compactum* (French and Russell).

The cutaneous lesions, usually limited to a single area, consist of densely aggregated nodules and plaques with a hard, verrucous surface.

Histopathology. The histologic appearance of the skin is very much like that of blastomycosis. The epidermis shows considerable hyperplasia although rarely to the extent that is usual in blastomycosis. The dermis shows an intensive infiltration, with a polymorphous granulation tissue containing many Langhans giant cells and small abscesses composed of polymorphonuclear leukocytes. Tuberculoid formations may be present, but true tubercles and caseation are absent, just as in blastomycosis.

The causative organisms are found in Langhans giant cells as well as free in the tissue and are especially numerous in the abscesses. They appear as sclerotic, dark brown, thick-walled, usually spherical spores varying in size from 8 to 15 microns. They lie either singly or in chains or clusters (Fig. 108). Reproduction is by intracellular wall formation and splitting, not by budding. In some of the organisms, cross walls can be seen.

Differential Diagnosis. Chromoblastomycosis cannot be differentiated from blastomycosis except through the different appearance of the fungi. Just as blastomycosis, chromoblastomycosis differs from tuberculosis verrucosa cutis by the presence of a fungus in the tissue, and the absence of true tubercles and of caseation.

COCCIDIOIDOMYCOSIS (SAN JOAQUIN VALLEY FEVER)

Coccidioidomycosis is caused by *Coccidioides immitis*. It is endemic in the southwestern United States, especially in the San Joaquin valley of California, and in northern Mexico. Three forms are recognized: primary, intermediate and progressive (Duemling).

Primary coccidioidomycosis represents an acute respiratory infection. Development of erythema nodosum is not uncommon.

Intermediate coccidioidomycosis manifests itself as a chronic pneumonitis resembling pulmonary tuberculosis and ends in complete recovery. No cutaneous lesions occur.

Progressive coccidioidomycosis (coccidioidal granuloma) follows the primary form in a small percentage of cases after a varying length of time. It has a very high mortality. Many organs, especially the meninges, the lungs, the bones and the lymph nodes, may be involved. Cutaneous lesions are common. They consist either of verrucous and granulomatous nodules or of subcutaneous cold abscesses which may break through the skin.

Histopathology. The nodose lesions of primary coccidioidomycosis have the same histologic appearance as idiopathic erythema nodosum (Winer).

The verrucous and the granulomatous lesions of coccidioidal granuloma resemble blastomycosis in their histologic aspects. How-

ever, there is less tendency to abscess formation, and caseation necrosis may occur (Moore). The causative organisms are found free in the tissue as well as in Langhans giant cells. As a rule, they are present in large number.

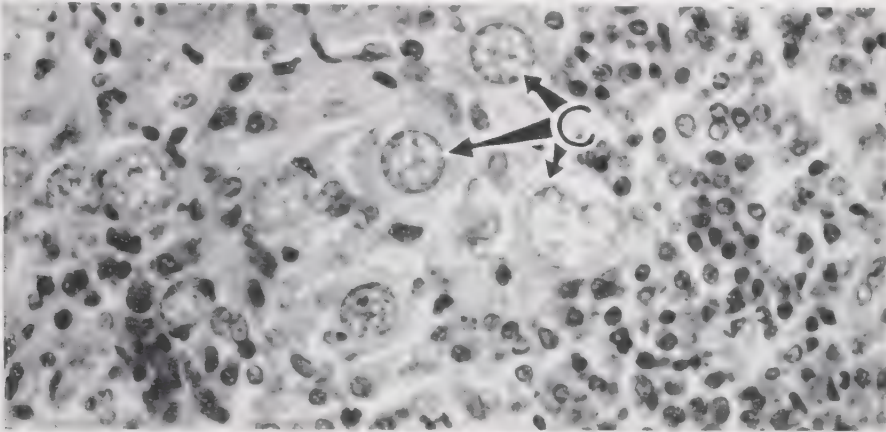


FIG. 109. *Coccidioidomycosis*. The *Coccidioides* spores (C) are large larger than those of other fungi—and show considerable variation in size. Their cytoplasm is granular. ($\times 400$)

The subcutaneous abscesses of coccidioidal granuloma resemble scrofuloderma in their histologic appearance. Surrounding a central area of necrosis, one observes a granulomatous infiltrate which is tuberculoid in type and composed of lymphocytes, plasma cells, epi-

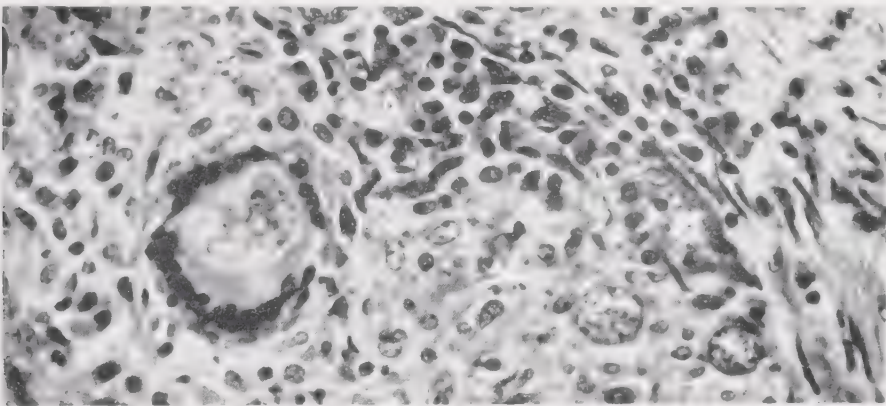


FIG. 110. *Coccidioidomycosis*. A large *Coccidioides* spore lies within a giant cell. The *Coccidioides* spore contains numerous endospores. ($\times 400$)

thelioid cells and some giant cells. Numerous spores are present extracellularly as well as intracellularly in giant cells.

The spores of *Coccidioides immitis* vary greatly in size, from 10 to 80 microns (Fig. 109). The average size is about 40 microns. Thus,

Coccidioides is much larger than *Blastomyces*, *Torula* or *Phialophora*. The spores are spherical and thick-walled and have a granular cytoplasm. Multiplication is not by budding but by formation of endospores which may be seen lying inside the larger spores (Fig. 110). The endospores are released into the tissue by rupture of the wall of the spore. Endospores may measure up to 5 microns in diameter.

Differential Diagnosis. A diagnosis of coccidioidomycosis can be made only in the presence of the fungus.

ACTINOMYCOSIS

Actinomycosis is caused either by *Actinomyces bovis*, which is anaerobic or micro-aerophilic, or by several species of *Nocardia* (e.g., *N. asteroides*, *N. madurae*), which are aerobic.

Actinomycosis frequently affects the skin. Involvement may be primary, as in Madura foot (mycetoma). More often, however, the infection reaches the skin from an internal focus. The most common form is cervicofacial actinomycosis, in which case the organism reaches the skin from the mouth; next in frequency are actinomycosis of the thoracic skin secondary to involvement of a lung and actinomycosis of the abdominal skin secondary to involvement of the cecum or the appendix.

The involved skin is dark red in color, possesses a "wooden" type of hardness and shows numerous sinuses discharging a serosanguineous or purulent fluid containing sulfur-yellow granules which consist of masses of fungi.

Histopathology. Histologic examination shows extensive granulation tissue containing large abscesses. The fungus granules are found within the abscesses. The granulation tissue is nonspecific in its appearance. In the early phase of the disease, it is composed of neutrophils, eosinophils, lymphocytes, plasma cells, histiocytes and fibroblasts. In the healing phase, fibroblasts predominate. Thus, the diagnosis can be established only by finding the *Actinomyces* granules in the abscesses. When selecting an area for biopsy, an area containing purulent material should be chosen.

The fungus granules are large and may measure several hundred microns in diameter, large enough to be visible macroscopically as the so-called sulfur granules. In histologic sections, they appear basophilic and irregularly lobulated (Fig. 111). They are homogeneous in the center and have radiating, branching filaments at the periphery. The ends of the filaments frequently are surrounded by a gelatinous sheath, giving the ends a club-shaped appearance. The filaments are much better seen in sections stained by Gram's method, which stains them Gram-positive, than in sections stained with routine stains. The

cells immediately around the granules are usually polymorphonuclear leukocytes, but foreign-body giant cells occasionally are seen in contact with the granules.

In general, *Nocardia* produces more necrosis and less granulation tissue and less fibrosis than *Actinomyces*. The granules of *Nocardia* are smaller and much less numerous than those of *Actinomyces* so that multiple sections are necessary to find them (Weed and Baggen-

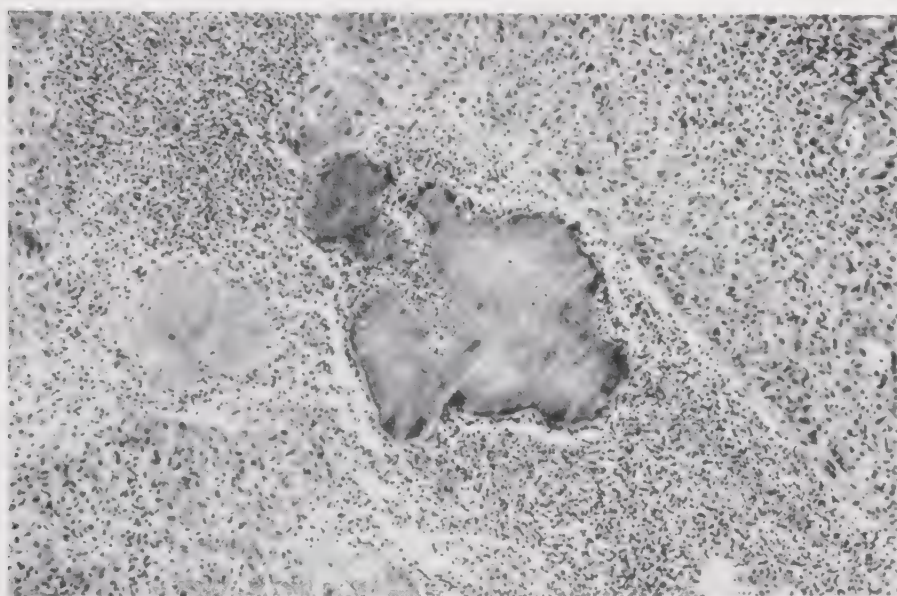


FIG. 111. Actinomycosis. A large "sulfur granule" is shown in the center of the field. The granule appears homogeneous in the center. "Clubs" are present at the periphery. ($\times 100$)

stoss). Nevertheless, these differences are not sufficiently distinct and cultural studies are necessary for a differentiation of *Nocardia* from *Actinomyces*.

SPOROTRICHOSIS

Sporotrichosis, caused by *Sporotrichum schenckii*, affects only the skin and the subcutaneous tissue, and thus is a benign disease. Most frequently encountered is the localized type of infection. In that type, there is a primary lesion (sporotrichotic chancre) which is commonly an ulcer but may be papillomatous. Secondarily, multiple subcutaneous nodules appear along the lymphatics draining the area. The nodules undergo suppuration with subsequent ulceration.

Much less common than the localized type of infection is the disseminated type, in which there are widely scattered lesions consisting of subcutaneous nodules which, like those of the localized type, form abscesses and may ulcerate (Moore and Kile).

Histopathology. The primary lesion of sporotrichosis shows a non-specific granulation tissue containing, among other cells, many plasma cells, epithelioid cells and some Langhans giant cells. Foci of suppuration are present. If the primary lesion is papillomatous, one finds, in addition, marked epithelial hyperplasia and intra-epidermal abscesses (Moore and Ackerman).

The subcutaneous nodules show a more characteristic appearance than the primary lesion because of the arrangement of the infiltrate

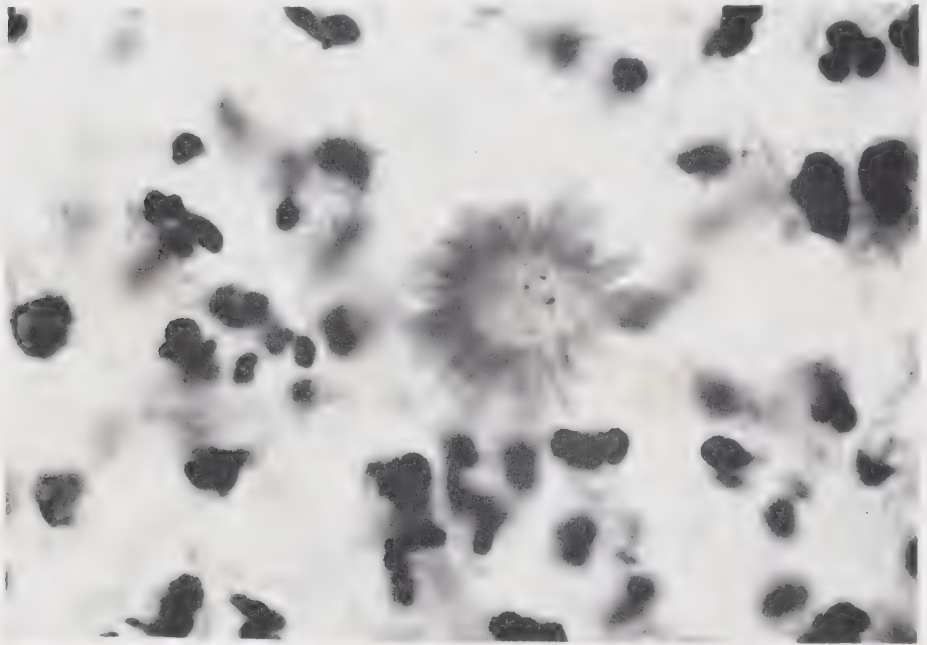


FIG. 112. *Sporotrichosis*. A large spore with radiating "asteroid" elongations is shown. ($\times 1350$) (Hermann Pinkus, M.D.)

in three zones—the chronic suppurative zone, the tuberculoid zone and the syphiloid zone. The zone in the center of the nodule, the chronic suppurative zone, is composed chiefly of neutrophils with a few histiocytes and lymphocytes. Small abscesses composed entirely of neutrophils are present within this zone. The middle or tuberculoid zone is characterized by numerous epithelioid cells and a large number of giant cells of the Langhans type. The giant cells may lie in groups. The peripheral or syphiloid zone consists of a richly cellular infiltrate of plasma cells, lymphocytes and fibroblasts. The zonal arrangement is not always distinct. In older nodules one merely sees a nonspecific granuloma.

The causative organisms are present in the tissue in small numbers as round to fusiform bodies which do not stain with hematoxylin and eosin but become visible when the periodic acid-Schiff reagent is employed (Kligman and Baldrige). In rare instances, a few large,

thick-walled, round spores are found free in the tissue, visible even with hematoxylin-eosin staining. Some of them have radiating "asteroid" elongations (Fig. 112) (Moore and Ackerman; Pinkus and Grekin).

Differential Diagnosis. Without the demonstration of the fungus, a diagnosis of sporotrichosis cannot be made but can only be suspected. The subcutaneous nodules of tularemia may have the same histologic appearance. Erythema induratum differs from sporotrichosis by its vascular changes and the presence of caseation, which is absent in sporotrichosis.

HISTOPLASMOSIS

Histoplasmosis, caused by the fungus *Histoplasma capsulatum*, in most instances is a fatal systemic disease. Occasionally, the disease is limited to the skin or the mucous membranes and benign in its course (Curtis and Grekin).

In the systemic form of histoplasmosis, the clinical picture is variable. The lymph nodes are often enlarged markedly. Pulmonary and adrenal involvement may be a prominent feature. Cutaneous or mucomembranous lesions occur in about half the patients with the systemic form of infection (Miller, Keddie, Johnstone and Bostick).

Several authors have reported the simultaneous occurrence of histoplasmosis and lymphoma, such as Hodgkin's disease (Ende, Pizzolato and Ziskind) and lymphatic leukemia (Cawley and Curtis). It is likely that the fungus infection occurs secondary to the lymphoma, especially in view of the fact that also torulosis has been observed in association with lymphoma (see page 224).

The skin lesions of histoplasmosis in both the systemic and the cutaneous form may be nodular, granulomatous or ulcerative.

Histopathology. Histologic examination reveals a chronic, non-specific, granulomatous infiltrate with foci of necrosis. Throughout this infiltrate, but especially in the vicinity of the necrotic foci, one observes large histiocytes (macrophages) engorged with numerous organisms.

Histoplasma capsulatum appears in sections stained with hematoxylin and eosin as a round or oval, basophilic body surrounded by a clear halo or capsule. Including this capsule, the organism measures from 2 to 4 microns in diameter. On staining with the periodic acid-Schiff reaction, however, *Histoplasma capsulatum* shows no capsule, but, instead, the body appears larger and lined by a definite, red-stained cell wall. Therefore, it appears that the so-called halo or

capsule is an artefact produced by plasmolysis which causes the cytoplasm to shrink away from the cell wall (Kligman and Baldrige). *Histoplasma capsulatum* is a fungus according to its cultural characteristics and because it multiplies by budding.

Differential Diagnosis. The general appearance of the granulomatous infiltrate with its parasitized histiocytes is much like that of rhinoscleroma, granuloma inguinale and cutaneous leishmaniasis. (For their differential diagnosis, see Table 5, page 237.)

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14

Diseases Caused by Protozoa

LEISHMANIASIS

Two types of leishmaniasis affect the skin: first, the type seen in the Old World, called cutaneous leishmaniasis, oriental sore or Delhi boil, and caused by *Leishmania tropica*, and, second, the type seen in the New World, called mucocutaneous leishmaniasis or South American leishmaniasis, and caused by *Leishmania braziliensis*. *Leishmania tropica*, *Leishmania braziliensis* and *Leishmania donovani*, which causes kala-azar, cannot be differentiated morphologically. However, they differ immunologically.

Cutaneous leishmaniasis is a benign, self-limited disease. It shows usually one, rarely several, ulcers, which are located on a hyperemic and infiltrated base and are covered with a thick, adherent crust. Healing takes place usually within from 2 to 12 months.

Mucocutaneous leishmaniasis is a more serious infection which may even result in death. It starts with a cutaneous ulcer which eventually heals. After a latent period of several years, late manifestations consisting of extensive granulomatous and ulcerative lesions appear not only on the skin but also on the mucous membranes of the mouth and the nasopharynx.

Histopathology. The lesions of cutaneous and of mucocutaneous leishmaniasis do not differ histologically except for the number of organisms present. In cutaneous leishmaniasis, the number of organisms is very large in early lesions but small in older lesions undergoing fibrosis. In mucocutaneous leishmaniasis, the number of organisms is always small. Often their detection is difficult and culture studies are necessary to prove their presence.

In both types of leishmaniasis, the epidermis may show marked acanthosis but it may be absent because of ulceration. In early lesions, the dermis contains a granulomatous infiltrate consisting mainly of histiocytes and plasma cells and some lymphocytes, neutrophils and eosinophils. In older lesions, the infiltrate tends to be tuberculoid. The diagnosis of leishmaniasis thus can be made only by identifying the causative organism which occurs in the tissue as so-called Leishman bodies.

Leishman bodies are present mainly within the histiocytes, but are found also extracellularly. The parasitized histiocytes often measure 20 microns or more in diameter and may contain several dozen Leishman bodies (Fig. 113).

The Leishman bodies, which represent a protozoon, appear in sections as round or oval bodies varying from 2 to 4 microns in diameter. They possess no capsule. Within the body, there is a relatively large,

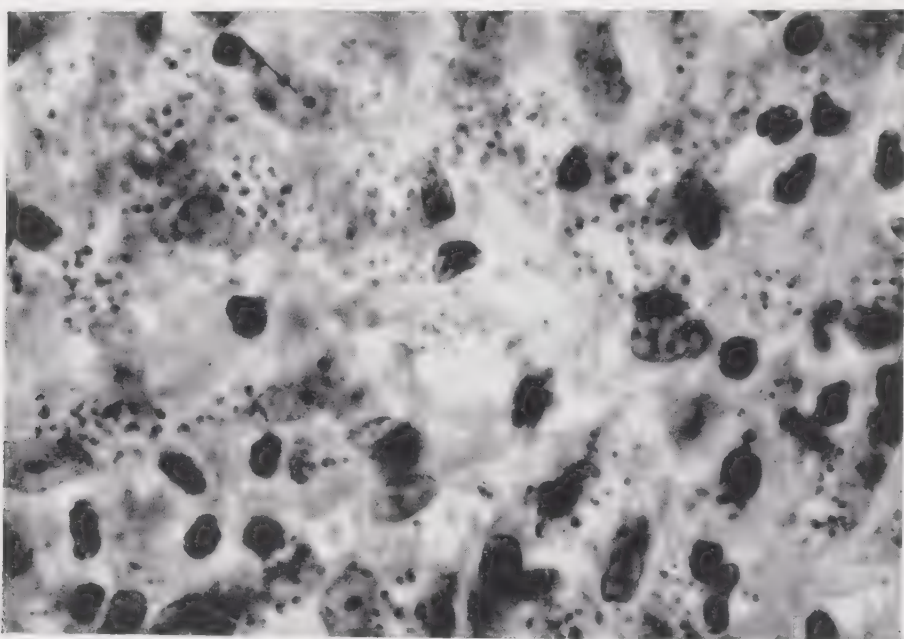


FIG. 113. Cutaneous leishmaniasis. Numerous Leishman bodies are present within histiocytes and free in the tissue. Leishman bodies possess a nucleus and a small paranucleus. ($\times 400$)

peripherally placed nucleus and, in addition, a small rodlike or oval paranucleus set at a tangent to the nucleus. The paranucleus, also called kinetoplast or blepharoplast, produces the flagella when the protozoon changes into the flagellate form outside the human body. Although visible in routine stains, Leishman bodies are seen best when Giemsa's stain is employed. With this stain, the nucleus and the paranucleus appear bright red.

Differential Diagnosis. The Leishman bodies easily can be differentiated from other parasites by the presence of a nucleus and a paranucleus within the organism.

It may be pointed out that four cutaneous diseases are characterized by a granulomatous infiltrate containing large parasitized histiocytes. They are rhinoscleroma and granuloma inguinale caused by bacteria, histoplasmosis caused by a fungus and leishmaniasis caused by a protozoon. In spite of great similarities, these four diseases have

points of differentiation which in most instances make a histologic diagnosis possible (see Table 5).

TABLE 5.—POINTS OF DIFFERENTIATION BETWEEN 4 CUTANEOUS DISEASES HAVING A SIMILAR GRANULOMATOUS INFILTRATE AND PARASITIZED HISTIOCYTES

DISEASE	DISTINCTIVE FEATURES IN THE HISTOLOGIC APPEARANCE OF THE INFILTRATE	SIZE OF THE ORGANISM (MICRONS)	APPEARANCE OF THE ORGANISM IN THE TISSUE
Rhinoscleroma.	Mikulicz cells, on the average, are larger than the parasitized histiocytes in the other three diseases. There are more plasma cells than in the other three diseases. Russell bodies are present	2-5	Encapsulated round or oval bodies
Histoplasmosis.	Foci of necrosis are common	2-4	Encapsulated round or oval bodies
Granuloma inguinale	Small abscesses composed of polymorphonuclear leukocytes are scattered through the infiltrate	1-2 (smaller than in the other three diseases)	Encapsulated round or oval bodies
Cutaneous leishmaniasis		2-4	Not encapsulated round or oval bodies containing a nucleus and a paranucleus

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15

Diseases Caused by Viruses

Viruses differ from bacteria by their smaller size and their inability to carry on biologic oxidation. The size of various viruses differs from near imperceptibility, so that they can be seen only in the electron microscope, to 0.35 micron. Those approximating the latter size, as, for instance, the virus of molluscum contagiosum, can be seen under an ordinary microscope. Because of their inability to carry on biologic oxidation, viruses can multiply only in living cells and cannot be cultivated on the usual artificial media. Some viruses can be grown on the chorio-allantoic membrane of the chick embryo (Goodpasture, Woodruff and Buddingh).

On histologic examination, intracellular inclusion bodies can be found in most virus diseases. These inclusion bodies represent colonies of the virus enveloped in a matrix (Goodpasture, Woodruff and Buddingh; Bland and Robinow; Ebert and Otsuka). The virus organisms within the inclusion bodies are often referred to as elementary bodies. The inclusion bodies are known under different names. They are, for instance, called Guarnieri bodies in variola, Lipschütz bodies in varicella, herpes zoster and herpes simplex and molluscum bodies in molluscum contagiosum. Since Paschen first demonstrated the presence of viruses or elementary bodies in the Guarnieri inclusion bodies of variola, the elementary bodies in variola frequently are referred to as Paschen bodies.

VARIOLA, VARICELLA, HERPES ZOSTER, HERPES SIMPLEX

These four diseases will be discussed together because the structure of the vesicles is very similar in all four of them.

The causative virus is present in the vesicles of all four diseases. The viruses of variola and herpes simplex can be grown on the chorio-allantoic membrane of the chick embryo if the membrane is inoculated with vesicle fluid, whereas the viruses of varicella and herpes zoster cannot be grown. However, Goodpasture and Anderson as well as Blank, Coriell and Scott have succeeded in infecting human

epidermis grafted on the chorio-allantois of chick embryos with the fluid obtained from herpes zoster vesicles.

It is probable that the viruses of varicella and herpes zoster are identical. There exists strong clinical evidence (Bruusgaard) and experimental evidence (Brain) for this contention. Furthermore, the two viruses have an identical appearance under the electron microscope (Baldrige, Blank and Rake). Wise and Sulzberger believe that herpes zoster represents an immune or allergic form of varicella which occurs in patients who had previous clinical or subclinical varicella.

Clinical Appearance. Variola shows a generalized eruption which at first consists of papules. After two or three days, the papules are transformed into vesicles which are characteristically umbilicated. After three more days, the vesicles change into pustules. In severe cases, in addition, there may be purpuric lesions. It is characteristic of variola that all lesions are at the same stage of development.

The eruption of varicella is also generalized. The lesions begin as small papules which soon develop into vesicles. The vesicles crust over, as a rule, without changing into pustules. Lesions occur in successive crops so that one observes lesions in different stages of development.

In herpes zoster, groups of vesicles are situated on an inflammatory base and arranged along the course of a sensory nerve. Ulceration of the lesions occurs occasionally. In rare instances, in addition to the localized eruption, there is a generalized vesicular eruption indistinguishable from that of varicella. Herpes zoster (especially the generalized form) is apt to occur in lymphoma (see page 491).

Herpes simplex shows one or several groups of vesicles on a mildly inflammatory base. The eruption may occur anywhere on the skin but is found most commonly about the face and the genitalia.

Histopathology. The characteristic histologic lesion in the four diseases is an intra-epidermal vesicle produced by profound degeneration of epidermal cells. Because of the presence of these degenerative changes, the vesicle differs histologically from those seen in other vesicobullous diseases (see "Classification of Bullae," page 66) and is easily recognized as virogenic. However, it is important that, as in all vesicobullous diseases, an early lesion be selected for biopsy; otherwise, secondary changes—especially invasion of inflammatory cells—may obscure the diagnostic features. The degeneration of the epidermal cells occurs in two forms: ballooning degeneration and reticular degeneration.

Ballooning degeneration causes marked swelling of the epidermal cells. Such swollen cells, called balloon cells, have a homogeneous,

eosinophilic cytoplasm (Figs. 114, 115). They may have no nucleus, or may have one or many. Because of the fact that the balloon cells lose their intercellular bridges, acantholysis occurs and the cells become separated from one another. Unilocular vesicles result. The process of ballooning degeneration occurs mainly at the base of virus vesicles leading to a dissolution of the lower epidermis, so that, ulti-



FIG. 114. *Herpes zoster*. Low magnification. There is marked ballooning degeneration of the cells at the floor of the vesicle. The cells of a hair follicle, shown at the left, likewise show ballooning degeneration. Reticular degeneration, observed at the top of the vesicle, is only slight. Since this is an early lesion, no inflammatory reaction is present. ($\times 100$)

mately, the originally intra-epidermal vesicles become subepidermal in many places. Ballooning degeneration affects also the epithelial cells of hair follicles and sebaceous glands.

Reticular degeneration represents a process in which the epidermal cells become greatly distended due to intracellular edema so that the cell wall bursts. By coalescence of neighboring, similarly affected cells, a multilocular vesicle results, the septa of which are formed by the resistant cellular walls (Fig. 116). Reticular degeneration occurs mainly at the top and the periphery of virus vesicles. In older vesicles, the resistant cellular walls disappear and the multilocular vesicle then becomes unilocular. It may be pointed out that reticular degeneration is not specific for virus vesicles since it also occurs in the vesicles of dermatitis (see page 68).

The upper dermis shows edema and an inflammatory infiltrate, the severity of which depends on the stage of the disease and also on the severity of the case. In severe cases of any of the four diseases, extravasation of erythrocytes may occur.

Inclusion bodies are found in the degenerated epidermal cells in all four diseases. In varicella, herpes zoster and herpes simplex, they

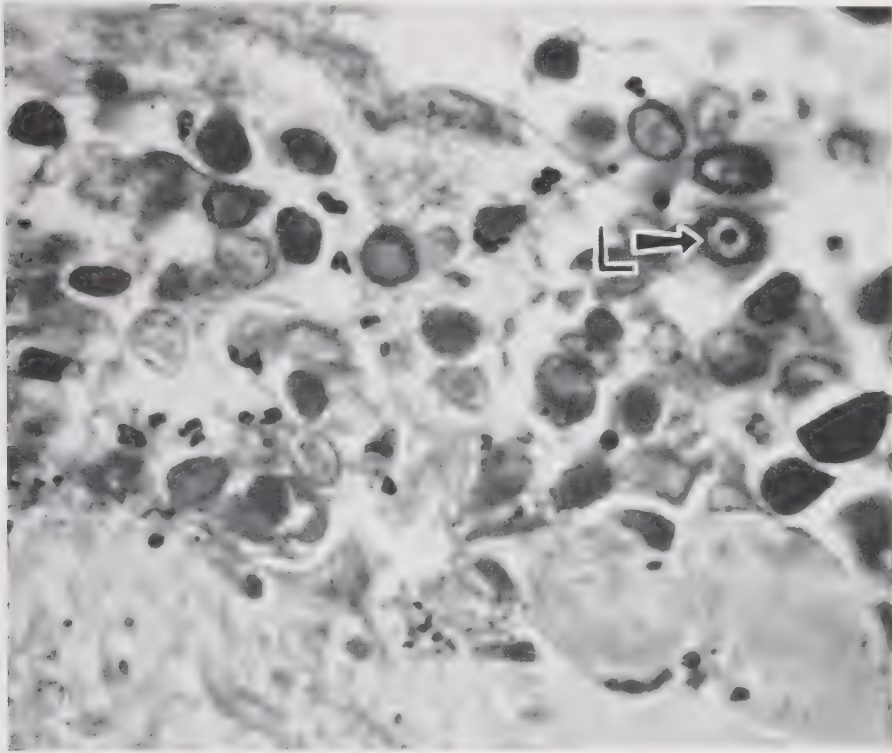


FIG. 115. Herpes zoster. High magnification of Figure 114. Balloon cells at the floor of a vesicle are shown. On the right side of the field, a Lipschütz inclusion body (which stains red) lies in the center of the nucleus of a balloon cell (L). The nuclear chromatin (which stains blue) is condensed at the margin of the nucleus. ($\times 400$)

are located exclusively within the nucleus, while in variola they lie predominantly in the cytoplasm but also within the nucleus. They are eosinophilic and Feulgen-negative (see page 30) in histologic sections. This is in contrast to the accepted fact that virus inclusion bodies are Feulgen-positive. However, experimental inoculations have shown that the cytoplasmic inclusion bodies of vaccinia (Bland and Robinow) and the intranuclear inclusion bodies of herpes simplex (Crouse, Coriell, Blank and Scott) are basophilic and Feulgen-positive at first and only later become eosinophilic and Feulgen-negative. Furthermore, the elementary bodies of variola, when tested in bulk in a test tube, give a positive Feulgen reaction, allowing the

conclusion that their negative reaction in a stained smear is due not to the absence, but to the low concentration, of deoxyribonucleic acid (DNA) in them (Bland and Robinow).

Whereas varicella, herpes zoster and herpes simplex are indistinguishable histologically, variola differs somewhat from them not only in the different location of the inclusion bodies but also in the structure of the vesicle.

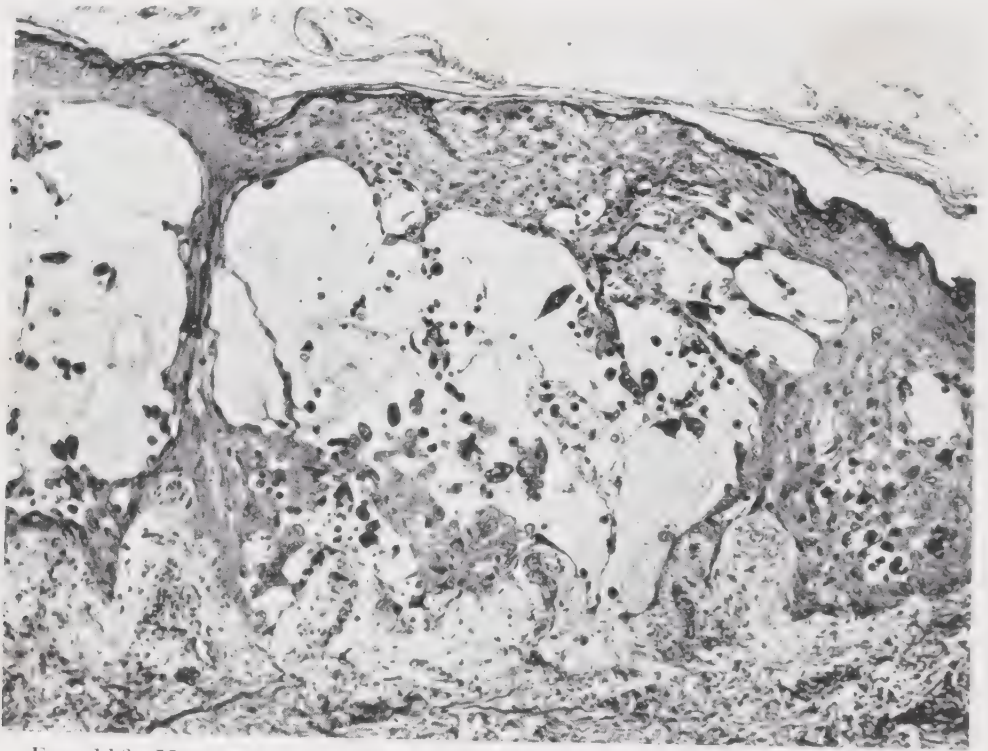


FIG. 116. **Herpes zoster.** Reticular degeneration is present, especially at the top of the vesicle, resulting in a multilocular vesicle. In addition, ballooning degeneration is present at the floor of the vesicle. ($\times 200$)

VARIOLA. In variola, reticular degeneration is prominent, at least in the early stage, and the balloon cells are few in number and small in size. Therefore, the vesicles are multilocular. In contrast, ballooning degeneration usually predominates in varicella, herpes zoster and herpes simplex. Nevertheless, the structure of the vesicle is no reliable criterion for differentiation of variola from the other three diseases since older vesicles of variola, through rupture of the septa, often become unilocular and, occasionally, in the other three diseases reticular degeneration is more pronounced than usual.

Cytoplasmic inclusions, however, occur only in variola and vaccinia (see page 244) and, if they are present, varicella, herpes zoster and herpes simplex can be excluded. They are numerous in the

early stage of the disease. In advanced lesions, intranuclear inclusions are also found, but only in small number. The viral nature of the cytoplasmic inclusions is well established. The relation of the intranuclear inclusions to the virus, however, is unknown, and it is possible that they are products of degeneration. They have not been observed in chorio-allantoic membranes infected with material from variola vesicles (Downie and Dumbell) and they do not occur in the lesions of vaccinia (see page 244).

The cytoplasmic inclusions, the so-called Guarnieri bodies, are round or oval, homogeneous, eosinophilic structures having a diameter up to 10 microns. They usually are surrounded by a clear, unstained zone or halo. The intranuclear inclusions are also eosinophilic. They usually lie in the center of the nucleus and are surrounded by an unstained halo, with the chromatin condensed at the periphery of the nucleus.

VARICELLA, HERPES ZOSTER, HERPES SIMPLEX. In these three diseases, ballooning degeneration (Fig. 114) is more prevalent than reticular degeneration and the vesicles usually are unilocular from the beginning except at the periphery and in the uppermost epidermis where reticular degeneration is apt to be present (Fig. 115). The intranuclear inclusions (Fig. 115) are like those seen in variola but they are present in much larger number, especially in multinucleated balloon cells. Often referred to as Lipschütz bodies, they are regarded as virus inclusion bodies.

Visceral lesions, in addition to those on the skin, occur in all three diseases with varying frequency.

Varicella, on rare occasions, has visceral lesions resulting in death (Johnson; Frank). On autopsy, areas of focal necrosis of epithelial cells with intranuclear inclusions may be found in many organs, but especially in the lungs, the pancreas, the liver, the intestinal tract, the renal tubules and the adrenal glands.

Herpes zoster shows in all cases involvement of the neural segment that corresponds to the cutaneous eruption. One finds: (1) severe inflammation of the posterior, sensory ganglion and of the posterior nerve roots, (2) peripheral mononeuritis, (3) unilateral, segmental poliomyelitis in the posterior columns of the cord, and (4) localized leptomeningitis (Denny-Brown and Adams). It is likely that the first localization of the virus occurs in the sensory ganglion (Head and Campbell). Degenerative changes in the sensory nerve fibers in the dermis, at the site of the cutaneous involvement, do not become apparent until 14 days after the appearance of the cutaneous eruption (Ebert).

Herpes simplex, in very rare instances, causes encephalitis, in which case inclusion bodies can be demonstrated in the nuclei of cerebral nerve cells (Smith, Lennette and Reames; Zarafonitis, Smadel, Adams and Haymaker).

Differential Diagnosis. Although the bullae or vesicles of pemphigus vulgaris show, like the virus vesicles, acantholysis and degeneration of epidermal cells, the two diseases easily can be differentiated because the ballooning degeneration in the virus vesicle is a far more profound degeneration than that occurring in the bullae of pemphigus vulgaris. Furthermore, virus vesicles are never seen in suprabasal location. The presence of inclusion bodies in the virus vesicles, of course, is another aid in differentiation.

ECZEMA VACCINATUM AND KAPOSI'S VARICELLIFORM ERUPTION

These two diseases occur only in patients with eczema, usually atopic eczema (Barton and Brunsting). Eczema vaccinatum is produced by the accidental inoculation of the vaccinia virus on eczematous lesions present on various parts of the body; and Kaposi's varicelliform eruption by the accidental inoculation of the virus of herpes simplex.

Clinically, both diseases look alike. They show a more or less extensive eruption composed of umbilicated vesicles and pustules situated chiefly in eczematous areas but also on otherwise normal skin. The face is usually the site of severest involvement and may show marked edema.

Histopathology. Both diseases present, on histologic examination, vesicles and pustules with evidence of reticular and ballooning degeneration (Lynch; Riley and Callaway). Because of the presence of innumerable inflammatory cells, especially neutrophils, the demonstration of inclusion bodies is often difficult. If they are found, they are located exclusively in the cytoplasm in eczema vaccinatum, and exclusively within the nucleus in Kaposi's varicelliform eruption.

Differential Diagnosis. Since eczema vaccinatum and Kaposi's varicelliform eruption do not differ in their clinical aspects and in the histologic structure of the bulla, and since demonstration of inclusion bodies may be impossible, the two diseases often must be differentiated on the basis of the history of possible exposure to the vaccinia virus and through isolation of the respective virus.

MOLLUSCUM CONTAGIOSUM

This disorder is characterized by the presence of a variable number of small, discrete, waxy, white or pink, globular, elevated nodules

with umbilicated centers. When fully developed, a small amount of a curdlike substance may be expressed from the center of the lesions.

Histopathology. In this disease, the epidermis grows down into the dermis as multiple, closely packed, pear-shaped lobules. Many epidermal cells undergo a peculiar form of degeneration as they gradually advance from the basal layer into the squamous, the granular

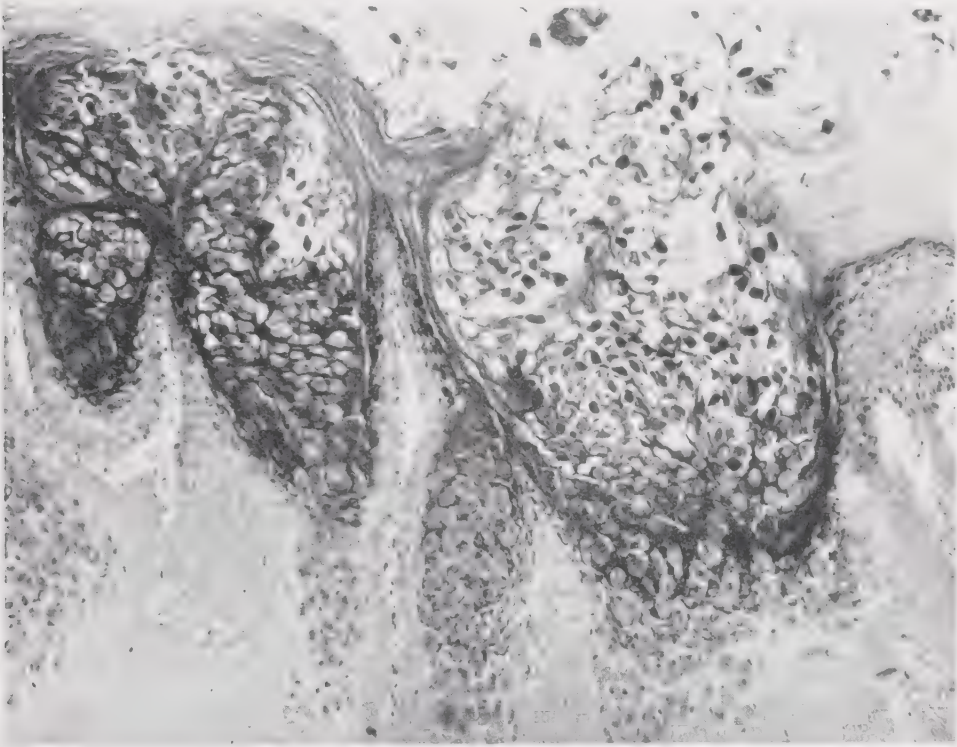


FIG. 117. *Molluscum contagiosum*. Numerous molluscum inclusion bodies are seen forming in the lower epidermis. They grow in size as they move toward the surface. ($\times 100$)

and the horny layers. Because of desquamation of the degenerated cells, a cavity forms at the surface, in the center of the growth (Fig. 117).

The degeneration of the epithelial cells is brought about by the formation of large cytoplasmic inclusion bodies which first appear as minute ovoid structures in the cytoplasm of some of the basal cells. They rapidly increase in size as the infected cells move toward the surface. When fully developed, the inclusion body greatly exceeds the original size of the invaded cell; it is then known as molluscum body. It displaces and compresses the nucleus which remains only as a thin crescent at the periphery of the cell. On the surface of the lesion, one finds numerous large inclusion bodies enmeshed within the horny layer.

The molluscum body is an inclusion body analogous to the Guarnieri body of variola. Embedded in a gelatinous matrix, it houses myriads of elementary bodies which are analogous to the Paschen bodies of variola and which represent the virus. In accordance with the fact that viruses, because of the presence of desoxyribonucleic acid (DNA), usually show a positive Feulgen reaction (see page 30) and stain basophilic with hematoxylin and eosin, the inclusion bodies, as they move from the lower epidermis to the horny layer during their development, become increasingly Feulgen-positive (Rake and Blank) and increasingly basophilic (see Plate 2).

The molluscum bodies measure up to 35 microns in diameter. The size of the virus is 0.35 micron (van Rooyen). The virus of molluscum contagiosum thus shares with the viruses of psittacosis and lymphogranuloma venereum the distinction of being the largest known to infect human beings. The virus of molluscum contagiosum does not grow on the chorio-allantois of the chick embryo.

VERRUCA

There are four types of verruca: verruca vulgaris, verruca plana, verruca plantaris and condyloma acuminatum. All four are caused

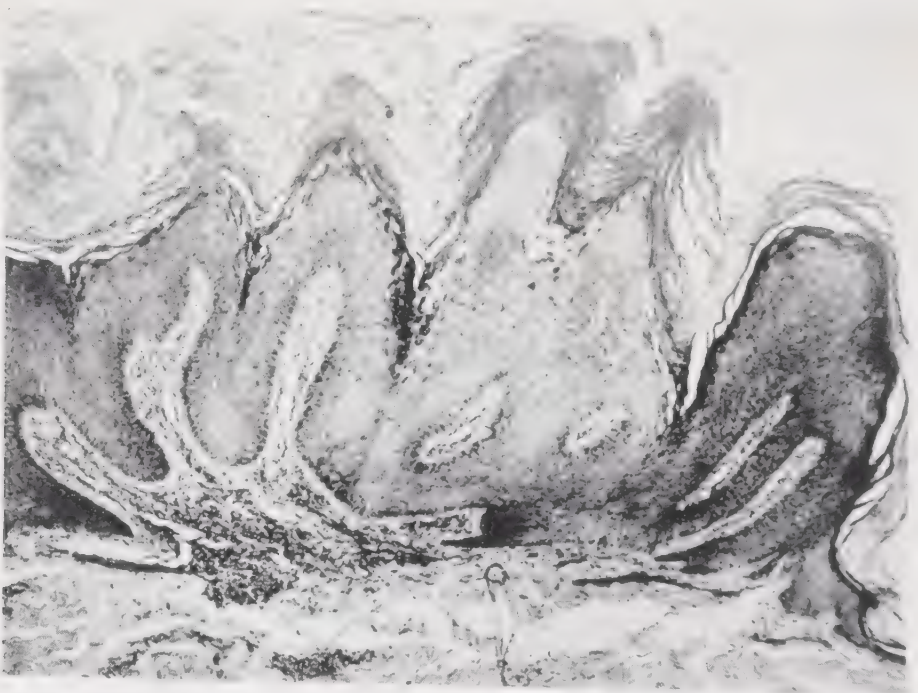


FIG. 118. *Verruca vulgaris*. Low magnification. There are hyperkeratosis, acanthosis and papillomatosis. The rete ridges are elongated and bent inward at both margins and thereby appear to point radially to the center. ($\times 100$)

by identical or allied strains of a virus. The virus does not grow on the chorio-allantoic membrane of chick embryos.

VERRUCA VULGARIS

Verrucae vulgares are circumscribed, firm, elevated growths having a papillomatous (verrucous) surface. Although they may occur

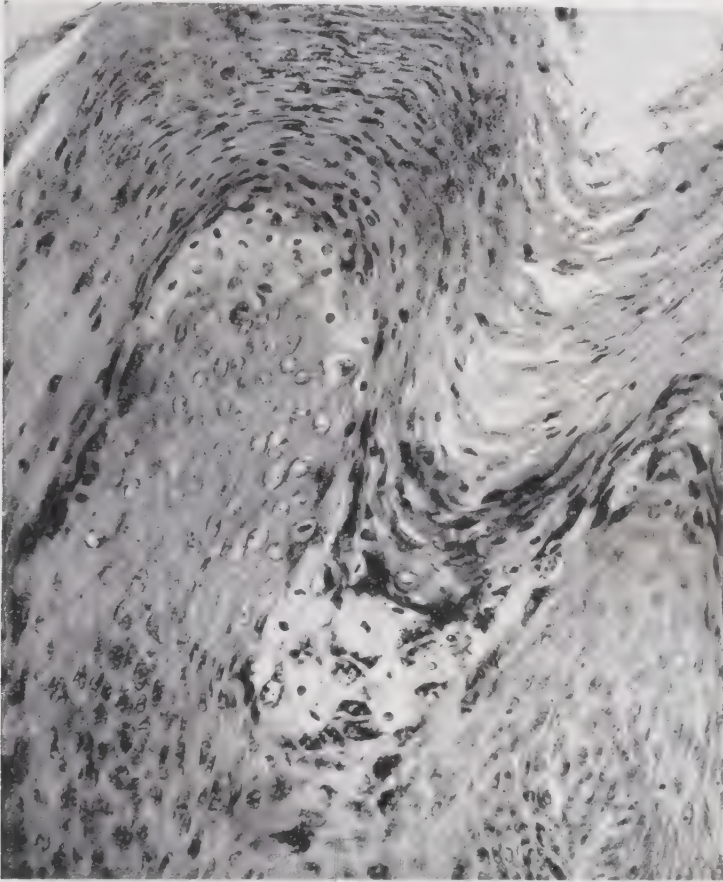


FIG. 119. *Verruca vulgaris*. High magnification of Figure 118. Groups of large, vacuolated cells lie in the upper stratum malpighii and in the granular layer. A tier of parakeratotic cells lies over the crest of a papillomatous elevation. ($\times 400$)

anywhere on the skin, the hands are the most common site of the lesions.

Histopathology. The lesions show hyperkeratosis with interspersed areas of parakeratosis, acanthosis and papillomatosis. The rete ridges are elongated and, at the margin of the verruca, often bent inward so that they appear to point radially toward a center (Fig. 118). The characteristic feature which distinguishes verruca vulgaris from other

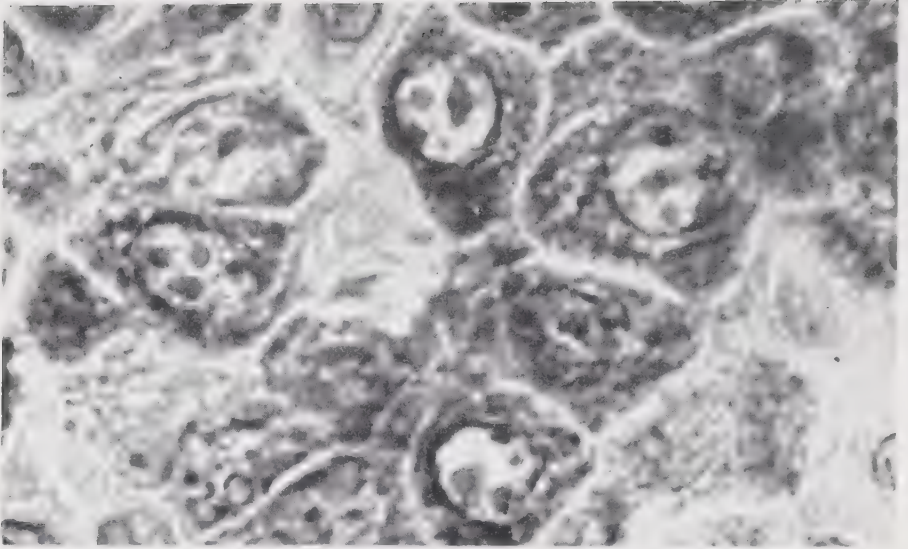


FIG. 120. *Verruca vulgaris*. The epidermal cells have large, vacuolated nuclei. Four of the nuclei contain a round, eosinophilic inclusion body. The darker particles present in these nuclei are nucleoli. ($\times 600$)

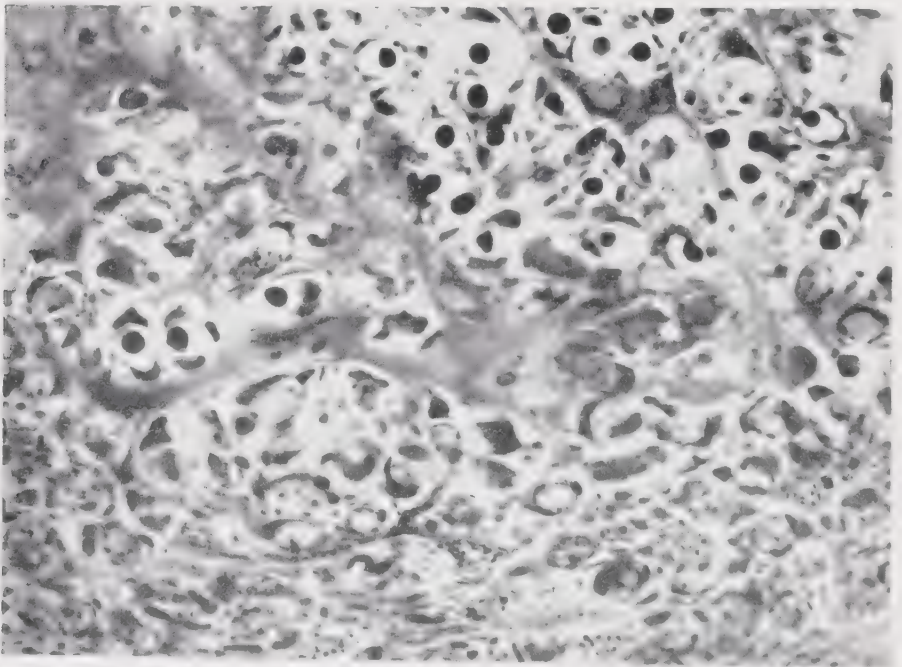


FIG. 121. *Verruca vulgaris*. In the lower portion of this illustration, the nuclei of the epidermal cells are vacuolated. In the upper portion, many of the nuclei are round, very deeply basophilic and surrounded by a clear zone. It has been suggested that these nuclei are filled with virus inclusion material. ($\times 200$)

papillomas (see page 322) is the presence of large, vacuolated cells in the upper stratum malpighii and in the granular layer (Fig. 119). However, these cells are regularly present only in young verrucae and may be missing in older ones. These large, vacuolated cells possess no intercellular bridges and even when located in the granular layer contain no keratohyaline granules. However, heavy clumps of keratohyaline granules are then often present in the unaffected granular cells found among them. The thickened horny layer contains many parakeratotic cells often arranged in tiers overlying the crests of the undulating stratum malpighii.

Although it has been proved through experimental inoculations with material filtered through Berkefeld candles that verrucae are caused by a virus (Wile and Kingery), the presence of a virus in histologic sections has not yet been demonstrated beyond any doubt. Nevertheless, two structures have been assumed by different observers to represent virus inclusion bodies.

Strauss, Bunting and Melnick regard round, eosinophilic bodies present in large, vacuolated nuclei of epidermal cells as virus inclusion bodies (Fig. 120). However, Blank, Buerek and Weidman regard these bodies as nucleoli since they give a negative Feulgen reaction (see page 30). They believe that another structure represents the virus in verrucae. They point out that many verrucae show in the granular layer cells with large, rounded, deeply basophilic nuclei surrounded by a clear zone (Fig. 121). They believe that these nuclei which give a strongly positive Feulgen reaction are completely filled with virus inclusion material. Yet, Lund and Leuchtenberger do not agree with this interpretation and believe that the large size and the hyperchromasia of these nuclei are but the result of an abnormal proliferation of nuclear chromatin. It may be pointed out that Strauss and his co-workers found the eosinophilic bodies described by them in only 4 per cent of the verrucae vulgares and 43 per cent of the verrucae plantares examined and never in lesions more than 9 months old. Blank and his co-workers found the changes described by them in 50 per cent of all verrucae. Their material consisted largely of verrucae vulgares.

Differential Diagnosis. For differentiation of verruca vulgaris from other papillomas, see page 322.

VERRUCA PLANA

Verrucae planae are slightly elevated, flat, smooth, angular papules. They may be the color of normal skin or have a yellowish brown hue. The face and the dorsa of the hands are affected most commonly.

Histopathology. Verruca plana shows hyperkeratosis and acanthosis, but, in contrast with verruca vulgaris, has no papillomatosis, only slight elongation of the rete ridges and no areas of parakeratosis. Furthermore, there is much more extensive vacuolization of epidermal cells (Fig. 122) than in verruca vulgaris.

In the upper stratum malpighii and in the granular layer, many of the cells are vacuolated. Some of the vacuolated cells are twice

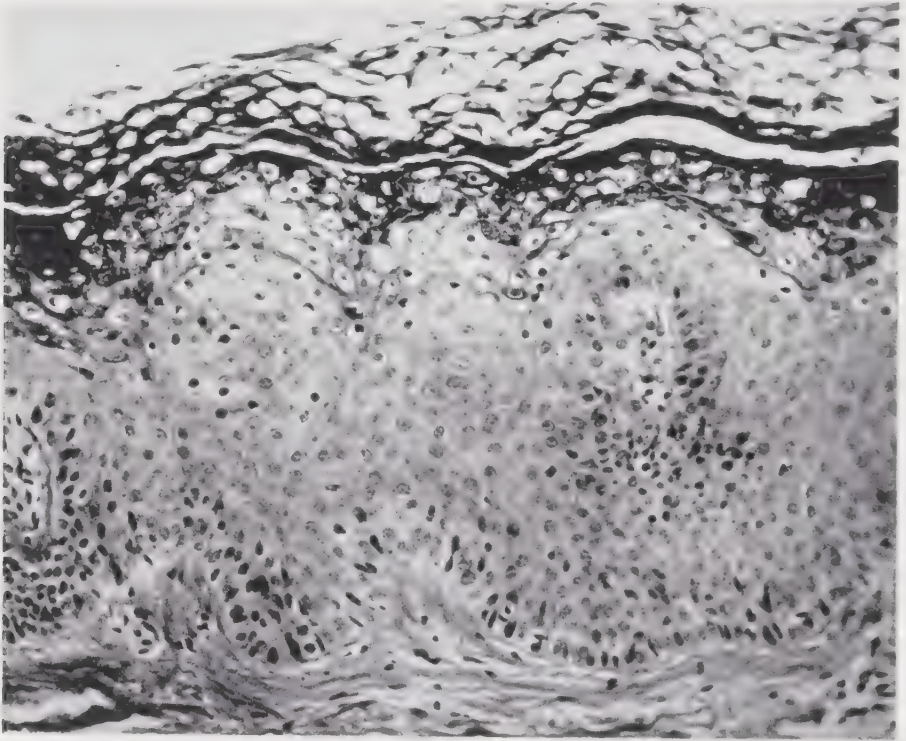


FIG. 122. Verruca plana. There are hyperkeratosis and acanthosis, but no papillomatosis. Numerous vacuolated cells lie in the upper stratum malpighii and in the granular layer. The horny layer has a "basket-weave" appearance. ($\times 200$)

their normal size. The nuclei of the vacuolated cells lie in the center of the cell and show some degree of pyknosis. The granular layer is uniformly thickened and the stratum corneum has a loosely felted, basket-weave appearance, due to vacuolization of the horny cells. The dermis appears normal. Some verrucae planae show a considerable amount of melanin in the basal layer (Becker).

The histologic picture of verruca plana resembles very closely that of epidermodysplasia verruciformis of Lewandowsky and Lutz (see "Epidermodysplasia Verruciformis," page 52). Although Lutz has expressed the conviction that the two conditions are identical, others still believe that they are unrelated.

VERRUCA PLANTARIS

Verrucae plantares occur on the soles of the feet. They are usually covered with a thick callus. Upon removal of the callus, they become visible as soft, granular, white or brownish tissue.

Histopathology. The histologic appearance of verruca plantaris resembles that of verruca vulgaris. However, the horny layer is much thicker and frequently shows extensive parakeratosis. The number of swollen, vacuolated cells in the upper stratum malpighii often is great in lesions of recent origin.

CONDYLOMA ACUMINATUM

Condylomata acuminata occur in the genital or the anal region as fairly soft, verrucous nodules which tend to coalesce into cauliflower-like masses.



FIG. 123. *Condyloma acuminatum*. There are parakeratosis and tremendous acanthosis. The cells of the stratum malpighii show marked intracellular edema and round, hyperchromatic nuclei. In the dermis, numerous dilated vessels and a dense, chronic inflammatory infiltrate are present. ($\times 50$)

Histopathology. The stratum corneum is only slightly thickened and is composed almost entirely of parakeratotic cells. There are papillomatosis and tremendous acanthosis, with thickening and elongation of the rete ridges. The rete ridges branch to such a degree that the picture of pseudo-epitheliomatous hyperplasia may result. However, squamous-cell carcinoma can be ruled out easily because the rete cells are in orderly arrangement and the border between epidermis and dermis is sharp (Fig. 123). The most characteristic feature, important for the diagnosis because it is nearly always present, is the marked vacuolization of many epidermal cells, especially in the upper half of the thickened epidermis. These vacuolated epidermal cells are larger than the other epidermal cells, have a very clear cytoplasm and, in their center, a deeply hyperchromatic, round or ovoid nucleus. These nuclei resemble those present in the parakeratotic horny layer of verrucae vulgares which are regarded by Blank, Buerk and Weidman as viral inclusion bodies.

The papillae are elongated and tortuous. They as well as the upper dermis contain numerous dilated capillaries and lymphatics, together with a rather dense chronic inflammatory infiltrate.

LYMPHOGRANULOMA VENEREUM (LYMPHOGRANULOMA INGUINALE, LYMPHOPATHIA VENEREA)

Lymphogranuloma venereum is a venereal disease caused by a virus. The virus grows well on the chorio-allantoic membrane of the chick embryo and in mouse brain.

The disease begins as a small initial papule on the genitals, which heals within a few days. After 2 weeks, the regional lymph nodes, in either the inguinal or the anorectal region, begin to enlarge. Abscesses form in the lymph nodes which, if the inguinal lymph nodes are affected, break through the skin and cause multiple draining sinuses.

Histopathology. The changes in the initial lesion on the genitals may be nonspecific or may consist of a central area of necrosis surrounded by epithelioid cells and a chronic granulation tissue containing many plasma cells (Kornblith).

In the lymph nodes, so-called stellate abscesses represent the characteristic lesion. They are diagnostic of the disease. As the earliest change in lymph nodes, one observes small islands of epithelioid cells scattered through the lymph node. They often contain a few giant cells of the Langhans type. The islands are embedded in a chronic granulation tissue containing many plasma cells. As the islands increase in size, their centers undergo necrosis and become filled with

numerous polymorphonuclear leukocytes as well as some macrophages (Sheldon and Heyman). These central abscesses tend to have a triangular or quadrangular shape with elongated corners, giving them a stellate appearance (Fig. 124). The epithelioid cells surrounding the abscesses are arranged in palisade formation. As the abscesses gradually enlarge, they coalesce and lose their stellate appearance.

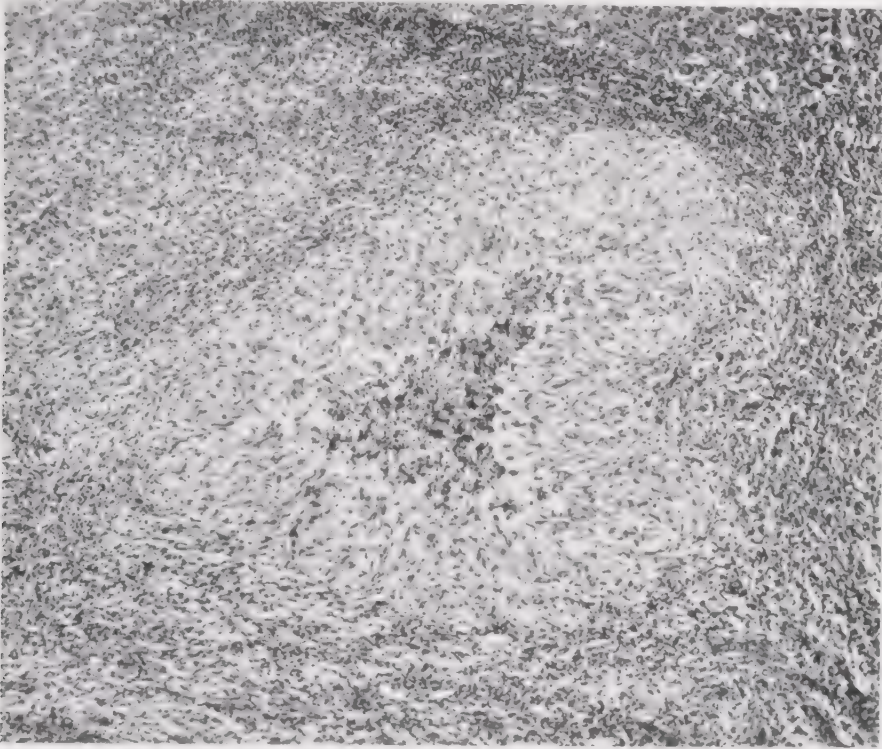


FIG. 124. *Lymphogranuloma venereum*. In the lymph node, a stellate abscess is present. It is surrounded by epithelioid cells in palisade formation. ($\times 100$)

MILKERS' NODULES

Milkers' nodules are acquired from cows infected with paravaccinia (natural cowpox). There are, usually on the fingers, one to three, and occasionally more nodules, 1 to 2 cm. in diameter, which are bluish red, semiglobular and usually painless. Spontaneous healing occurs in 1 to 2 months.

Histopathology. The epidermis shows acanthosis and parakeratosis. A dense, nonspecific chronic inflammatory infiltrate is present in the dermis. The capillaries are increased in number, are dilated and show swelling of their endothelial cells (Nomland and McKee).

While most authors have found no inclusion bodies, Katzenellenbogen observed them in some but not in all of his cases. They were

located in the cytoplasm of vacuolated epidermal cells and often were Feulgen-positive. Their appearance was similar to that of the inclusion bodies observed in variola and vaccinia.

Study of smears of tissue obtained from milkers' nodules under the electron microscope has shown the presence of typical elementary bodies of the paravaccinia type (Nasemann and Deubner).

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16

Metabolic Diseases

LIPOIDOSES

The term lipoidoses has been applied to a group of diseases in which the lesions, due to a local or generalized disturbance of the lipid metabolism, contain lipid substances.

No generally accepted classification of the lipoidoses exists. The following classification is based largely on the classifications published by Thannhauser and by Montgomery and Osterberg.

- I. Lipoidoses with Increased Blood Lipids
 1. Primary hypercholesteremic xanthomatosis
 2. Biliary xanthomatosis
 3. Idiopathic hyperlipemia
 4. Secondary hyperlipemia
- II. Lipoidoses with Normal Blood Lipids
 5. Lipid reticulo-endotheliosis (Hand-Schüller-Christian disease)
 - a. Fulminating type: Letterer-Siwe disease
 - b. Regular type: Hand-Schüller-Christian disease
 - c. Abortive type: eosinophilic granuloma
 6. Niemann-Pick disease (sphingomyelin lipoidosis)
 7. Gaucher's disease (kerasin lipoidosis)
 8. Lipoid proteinosis
 9. Extracellular cholesterosis
- III. Localized Lipoidoses
 10. Xanthelasma palpebrarum
 11. Necrobiosis lipoidica

LIPOIDOSES WITH INCREASED BLOOD LIPIDS

1. Primary Hypercholesteremic Xanthomatosis

Primary hypercholesteremic xanthomatosis is a familial disease characterized by high values for serum cholesterol and phospholipids but normal values for serum neutral fat. Therefore, the serum is clear.

Cutaneous lesions consist of flat or slightly raised xanthelasmata on the eyelids and tuberous xanthomata, especially on the elbows and the knees. In addition, there are tendon xanthomata, especially on the Achilles tendons, the patellar tendons, and the extensor ten-

dons of the hands. Atherosclerotic cardiovascular disease is common and may lead to death due to coronary occlusion in early life (Bloom, Kaufman and Stevens).

Histopathology. The histologic appearance of the cutaneous and the tendinous lesions is characterized by the presence of xanthoma or foam cells. Xanthoma cells are phagocytic cells filled with lipid drop-

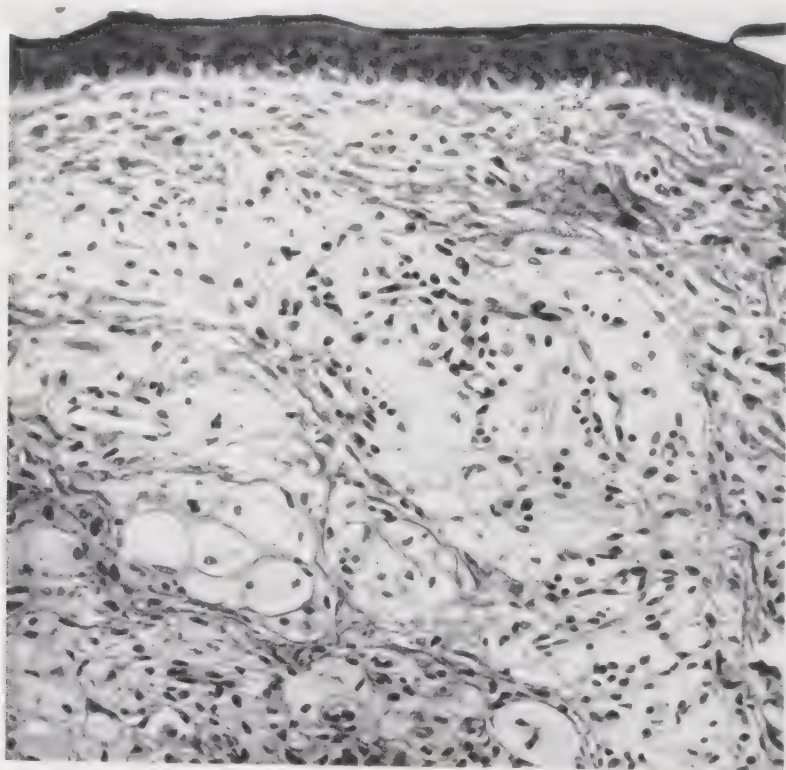


FIG. 125. *Xanthoma tuberosum*, early lesion. Numerous xanthoma cells (foam cells) are present. There is only little fibrosis. ($\times 200$)

lets. In routine sections, the lipid droplets have been dissolved and extracted in the process of fixation and embedding, so that the cells have a reticulated or foamy appearance (Fig. 125). However, the lipid droplets can be seen when formalin-fixed frozen sections are stained with fat stains, such as scarlet red (Fig. 126). With scarlet red, the lipid substance in the xanthoma cell stains a brownish red, in contrast to the lipid substance in sebaceous glands and the subcutaneous fat, which stains a bright orange-red. This is due to the fact that the lipid substance in xanthoma cells is predominantly cholesterol and phospholipids, whereas the lipid substance in the sebaceous cells and the subcutaneous fat cells is predominantly neutral fat. Polariscopic examination of frozen sections reveals the lipid droplets

in xanthoma cells to be anisotropic (doubly refractile) in contrast with the fat in the sebaceous cells and the subcutaneous fat cells, which is isotropic (not doubly refractile). (See page 31.)

Xanthoma cells form from perithelial cells, which are histiocytes. They have usually one nucleus, but may have two and even many

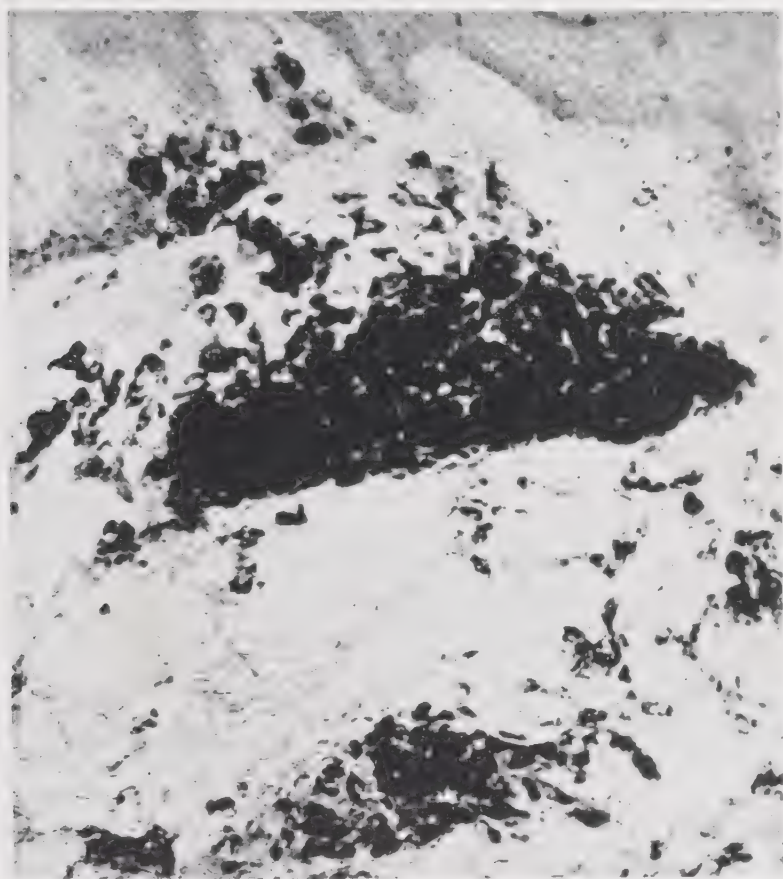


FIG. 126. Xanthoma tuberosum, early lesion. Scarlet-red stain for fat. The xanthoma cells are filled with lipid material. ($\times 100$)

nuclei. In multinucleated xanthoma cells, the nuclei either are irregularly distributed, as in foreign-body giant cells, or lie near the center of the cell grouped around a small island of nonfoamy cytoplasm and surrounded by foamy cytoplasm. This latter type is called Touton giant cell (Fig. 127).

In the skin, one finds xanthoma cells in small and large aggregates. In early lesions, there is usually an admixture of inflammatory cells, particularly polymorphonuclear leukocytes, lymphocytes and histiocytes. In well-developed lesions, the infiltrate is composed almost entirely of xanthoma cells (Fig. 125). Fat stains in this stage show

that all fat is intracellular. In involuting lesions, fibroblasts appear (Fig. 127). Ultimately, fibrosis replaces the foam cells. Weidman and Schaffer express the belief that the foam cells themselves can become transformed into fibroblasts. In old fibrosing lesions, cholesterol may be found not only in foam cells but also extracellularly.

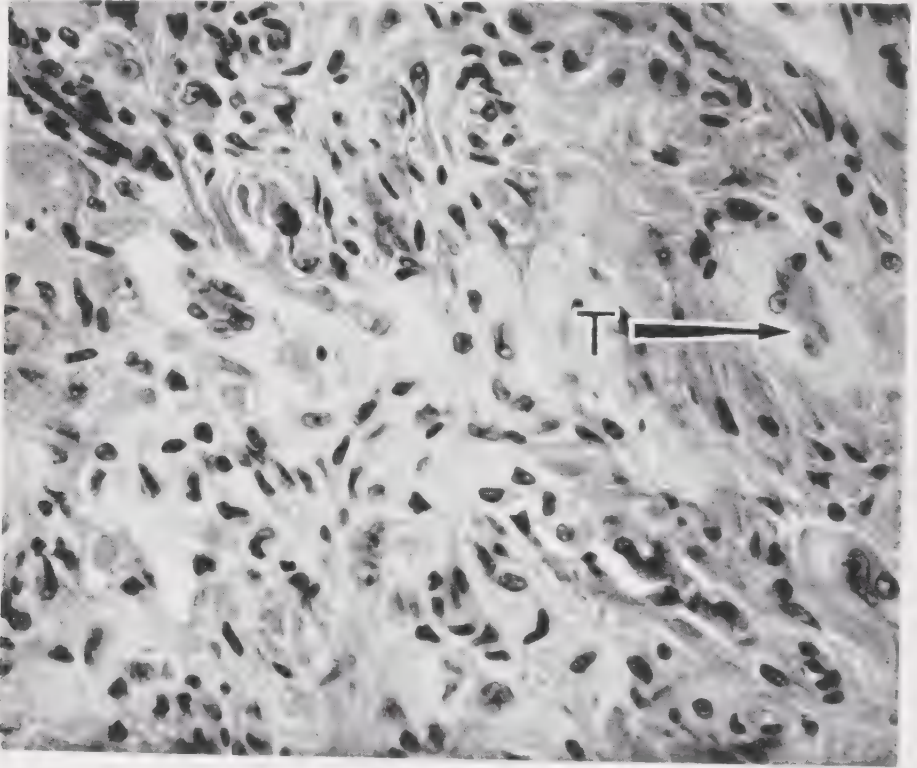


FIG. 127. **Xanthoma tuberosum, late lesion.** In addition to xanthoma cells, many fibroblasts are present. On the right side, there is a typical Touton giant cell (T). In the Touton cell, the nuclei lie near the center of the cell, grouped around a small island of nonfoamy cytoplasm and surrounded by foamy cytoplasm. ($\times 400$)

Differential Diagnosis. Differentiation between a fibrotic lesion of xanthoma tuberosum and histiocytoma may be very difficult and even impossible. It may be necessary to rely upon clinical and blood chemical data for the correct diagnosis (Montgomery and Osterberg).

2. *Biliary Xanthomatosis*

Biliary cirrhosis may cause high values for cholesterol and phospholipids in the serum and lead to xanthelasmata on the eyelids and tuberous xanthomata on the skin that are indistinguishable from those of primary hypercholesteremic xanthomatosis. However, deep jaundice is present and the jaundice precedes the appearance of

xanthomatous lesions often by many years. The blood serum is clear, but, due to its high content of bilirubin, it is intensely green.

The biliary cirrhosis which causes the xanthomatous lesions is produced, as a rule, either by cholangiolitis or by extrahepatic obstruction (MacMahon); but, occasionally in children, by congenital hypoplasia of bile ducts (MacMahon and Thannhauser).

Histopathology. The cutaneous lesions show the same histologic picture as is found in primary xanthomatosis.

3. *Idiopathic Hyperlipemia*

In idiopathic hyperlipemia, which usually is not familial, the blood serum shows an elevation not only of the cholesterol and phospholipids, as in primary hypercholesteremic xanthomatosis, but also of the neutral fat. Therefore, the blood serum is milky.

The cutaneous lesions are of two types: tuberous xanthomata, which are found especially on the elbows and the knees, and papular xanthomata, which may be diffusely distributed but are most prevalent on the buttocks. The papular xanthomata have a tendency to come and go and, therefore, are often referred to as eruptive xanthomata. Xanthelasmata of the eyelids are absent, but tendon xanthomata may occur (Lever, Smith and Hurley).

Visceral manifestations occasionally are present. They include: hepatosplenomegaly, attacks of abdominal pain due to secondary pancreatitis and coronary heart disease which, however, occurs less frequently than in primary hypercholesteremic xanthomatosis. The association of idiopathic hyperlipemia with hepatosplenomegaly occasionally is referred to as Bürger-Grütz disease.

Histopathology. The histologic appearance of the xanthomata in idiopathic hyperlipemia is the same as that of the xanthomata in primary hypercholesteremic xanthomatosis. The papular xanthomata which usually are of recent origin often show, like most young xanthomata, an admixture of inflammatory cells (see page 259).

Only few reports on the histology of the visceral lesions are available. In one patient with hepatosplenomegaly, conspicuous fat infiltration of the liver cells was observed on biopsy (Movitt, Gerstl, Sherwood and Epstein). The presence of pancreatitis in patients with attacks of abdominal pain has been confirmed repeatedly by exploratory operation (Klatskin and Gordon).

4. *Secondary Hyperlipemia*

Secondary hyperlipemia may occur secondary to severe diabetes ("xanthoma diabeticorum"), to nephrosis and to glycogen storage disease (von Gierke's disease). The amounts of cholesterol, phospho-

lipids and neutral fat in the serum are elevated and the serum is milky.

Papular eruptive xanthomata occur which usually are diffusely distributed but have a predilection for the buttocks. Occasionally, recently erupted papules have an inflammatory base.

Histopathology. The papular xanthomata of secondary hyperlipemia show the same histologic picture as other xanthomata. Since they usually are of recent origin, a rather marked inflammatory infiltrate may be present with large numbers of neutrophils. In the involuting stage, much of the cholesterol may be seen in phagocytes and extracellularly (Montgomery and Osterberg).

LIPIDOSES WITH NORMAL BLOOD LIPIDS

5. *Lipid Reticulo-endotheliosis (Hand-Schüller-Christian Disease)*

Letterer-Siwe disease, Hand-Schüller-Christian disease and eosinophilic granuloma represent variations in degree, stages of development and localization of the same basic disease process (Farber). Formerly, Hand-Schüller-Christian disease was regarded as a primary disturbance of the lipid metabolism, as a normocholesteremic xanthomatosis (Thannhauser and Magendantz), but this concept has been abandoned (Mallory) and the presence of cholesterol in the lesions is now regarded as a secondary infiltration. The three diseases are at present believed to be histiocytoses or reticulo-endothelioses. If the reticulo-endotheliosis occurs in infancy, it is generalized and rapidly fatal (Letterer-Siwe disease); death occurs before sufficient time has elapsed for the development of the lesion into a lipogranuloma. In early childhood, the disease is chronic (Hand-Schüller-Christian disease), and lipidization is, as a rule, pronounced. In later childhood or in the adult, the usual picture is that of eosinophilic granuloma, which represents an abortive form of the disease. Transitional cases between these three forms of reticulo-endotheliosis are common. The values for blood-plasma lipids are normal in all three forms.

LETTERER-SIWE DISEASE (NONLIPID HISTIOCYTOSIS OF FOOT AND OLCOTT). This disorder usually occurs in infants and is almost inevitably fatal within a few months. It is characterized by fever, anemia, enlargement of the liver and the spleen, lymphadenopathy and multiple defects of the bones. In most cases, cutaneous lesions are present. They may consist of petechiae, papules or pustules. In some cases, one observes numerous, closely set, brownish papules covered with scales or crusts. This type of eruption usually is extensive with a predilection to involve the scalp, the face and the trunk.

The resemblance of the eruption to seborrheic dermatitis and Darier's disease is often striking (Laymon and Sevenants).

Histopathology. The cutaneous lesions show, usually close to the epidermis and often invading into the epidermis (Fig. 128), accumulations of histiocytes (reticulum cells) intermingled with a few lymphocytes and varying numbers of eosinophils. Extravasated blood cells frequently lie in and about the masses of histiocytes. The histiocytes appear as large cells with irregularly shaped, vesicular nuclei and abundant, slightly eosinophilic cytoplasm (Fig. 129). In some areas, these cells are distinctly outlined and even separated by edema, but in other areas their cytoplasm is confluent. Occasionally, some of the cells have a foamy cytoplasm and stain positive for fat with fat stains. The epidermis may become destroyed by pressure of the underlying cells (Foot and Olcott; Abt and Denenholz; Lane and Smith, case 1).

The visceral lesions consist of proliferations of large, pale reticulo-endothelial cells which invade and replace the normal structure of spleen, liver, bone marrow, lymph nodes and other organs (Sweitzer and Laymon).

HAND-SCHÜLLER-CHRISTIAN DISEASE. Diabetes insipidus, exophthalmos and multiple defects of the bones, especially of the cranium, represent the triad of typical Hand-Schüller-Christian disease. However, any one or even all three of the cardinal symptoms may be absent, and involvement may occur in entirely different organs. For example, enlargement of the liver, the spleen and the lymph nodes is common and dwarfism is observed occasionally. Hand-Schüller-Christian disease takes a chronic course, usually extending over years, and has a mortality of about 70 per cent.

Cutaneous lesions are quite uncommon. If present, they are similar to those seen in Letterer-Siwe disease, consisting of an extensive eruption of coalescing, scaly or crusted papules with a distinct clinical resemblance to Darier's disease. Occasionally, the term xanthoma disseminatum is used for this eruption.

Histopathology. Early cutaneous lesions of Hand-Schüller-Christian disease show the same histologic picture as the cutaneous lesions of Letterer-Siwe disease (Lane and Smith; Laymon and Sevenants). In mature lesions, a large number of the histiocytes show a foamy cytoplasm, and typical foam cells may be present (Thannhauser and Magendantz). In old lesions, the number of foam cells again may be small and foreign-body giant cells may be found. As a rule, the tendency to lipidization is less pronounced in the cutaneous lesions than in the lesions of other organs.

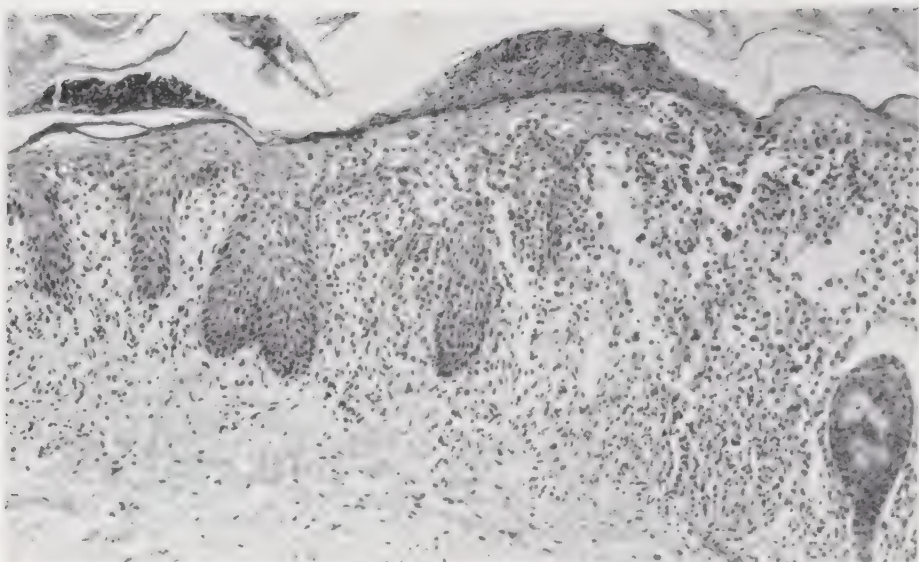


FIG. 128. Hand-Schüller-Christian disease (eosinophilic granuloma). Low magnification. The upper portion of the dermis contains an infiltrate composed almost entirely of loosely aggregated histiocytes. The infiltrate has invaded the epidermis in many areas. ($\times 100$)

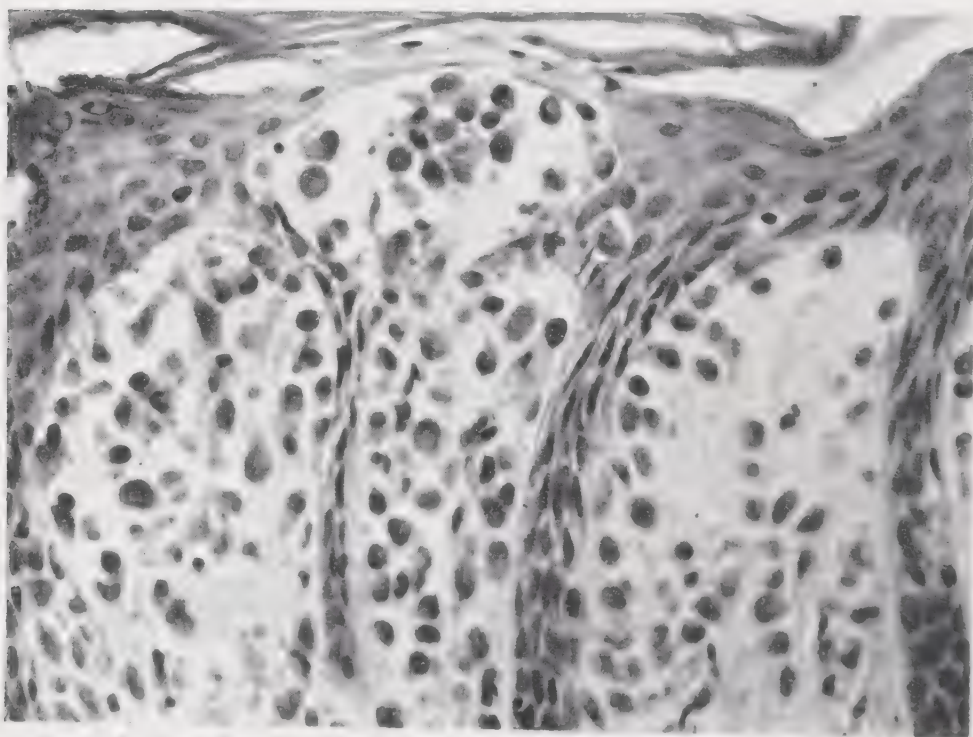


FIG. 129. Hand-Schüller-Christian disease (eosinophilic granuloma). High magnification. The histiocytes of the infiltrate possess irregularly shaped nuclei and abundant cytoplasm. In the center, the infiltrate has invaded the epidermis. ($\times 400$)

EOSINOPHILIC GRANULOMA. This is the third and least severe disease of this group. The lesions are either solitary or few in number. They occur, as a rule, in the bones. In rare instances, the skin is also involved. The cutaneous lesions consist either of an extensive eruption of crusted papules as in Letterer-Siwe and Hand-Schüller-Christian disease (Lever and Leeper) or of one or several erythematous granulomatous plaques which may undergo ulceration (Curtis and Cawley; McCreary). The two types of lesions may be present simultaneously. (Granuloma faciale, formerly called eosinophilic granuloma of the face, is an entirely different disease from eosinophilic granuloma and is not related to it. For its description, see page 111.)

Histopathology. The papules have the same histologic appearance as in Letterer-Siwe disease; namely, an infiltrate of loosely aggregated large histiocytes located in the upper dermis and invading the epidermis (Figs. 128, 129) (Lever and Leeper). The number of eosinophils is usually small.

The granulomatous plaques also show numerous loosely arranged large histiocytes within an edematous stroma. Eosinophils are present in varying numbers. They usually lie in patches rather than diffusely distributed through the lesion. In addition, a few lymphocytes and plasma cells are present (Curtis and Cawley; McCreary; Lever and Leeper).

Lipid is absent in the cutaneous lesions but may be present in the associated osseous lesions.

6. *Niemann-Pick Disease*

Niemann-Pick disease is characterized by abnormal deposits of sphingomyelin, a diaminophosphatide, in the reticulo-endothelial cells of many organs but not in the skin. The level of lipids in the blood serum is normal.

The disease occurs, as a rule, in Jewish infants and is fatal. There are enlargement of the liver and the spleen, cachexia and brownish discoloration of the skin.

Histopathology. On histologic examination, the brownish discoloration of the skin is found to be due to the presence of increased amounts of melanin.

7. *Gaucher's Disease*

In Gaucher's disease, kerasin, a cerebroside, is deposited in the reticulo-endothelial cells of many organs. The skin, however, is spared. The blood lipids are normal.

The disease tends to be familial, occurs predominantly in Jews, may start at any age and takes a chronic course. There is hepatosple-

nomegaly and rarefaction with cortical thickening of the long bones. The skin shows brownish discoloration.

Histopathology. The skin shows increased amounts of melanin.

8. *Lipoid Proteinosis (Urbach-Wiethe)*

Lipoid proteinosis is characterized by lipid infiltrations of the skin, of the oral mucosa and of the larynx. Although the blood lipids may

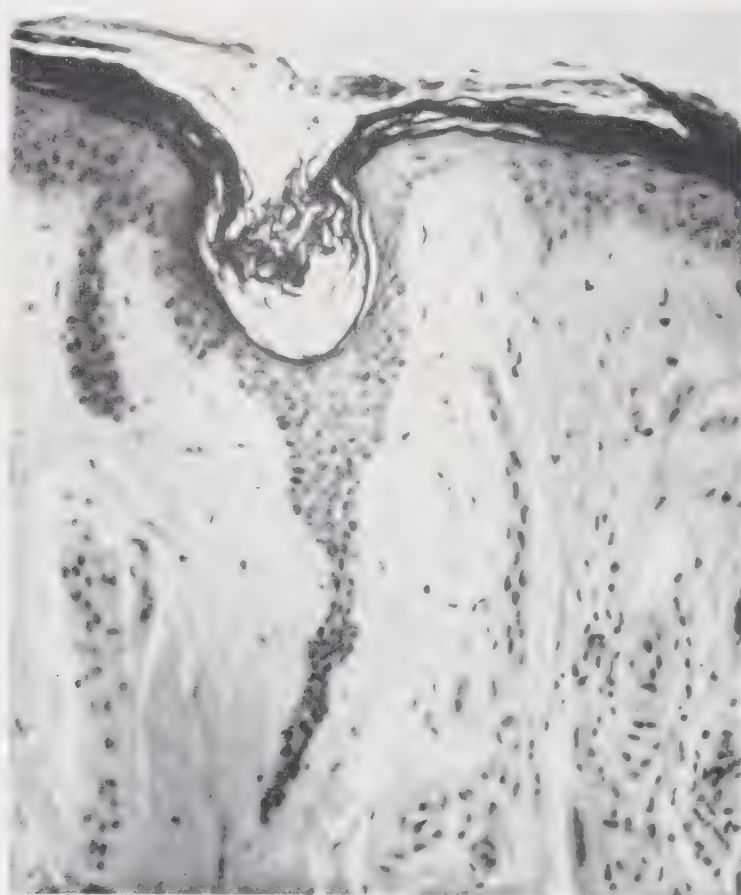


FIG. 130. **Lipoid proteinosis.** The dermis is occupied by thick, wavy, hyalin-like bundles which run perpendicular to the epidermis. In addition, the hyalin-like material surrounds all blood vessels as a thick mantle. ($\times 200$)

be normal (Wise and Rein; Price, LaRosa and Settle), there may be an increase in the total lipids (Hansen; Ramos e Silva) or a relative increase in phospholipids (Montgomery and Havens; Wile and Snow). The disease is often familial.

Clinically, one observes nodular and verrucous lesions on the skin and on the mucous membranes of the mouth and the larynx. The nodules of the skin, on regressing, leave pitted scars, giving the skin a

“pigskin-leather” appearance. The tongue is firm and there is hoarseness due to laryngeal lesions.

Histopathology. The histologic picture of the skin is striking and diagnostic. The epidermis shows hyperkeratosis and irregular acan-

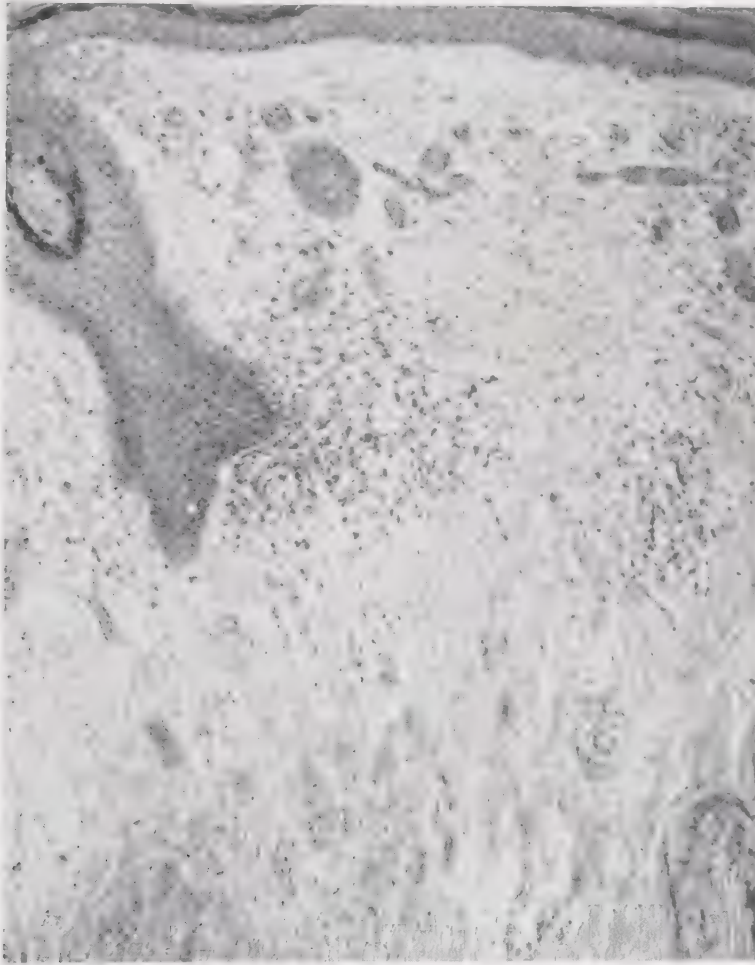


FIG. 131. **Lipoid proteinosis.** Scarlet-red stain for fat. A large amount of lipid material is present. It occurs in the form of small droplets throughout the hyaline material, particularly around the blood vessels. ($\times 100$)

thosis. The dermis is considerably thickened. The upper half of the dermis is occupied by thick, wavy bundles which are composed of a homogeneous, amorphous, hyalin-like material and stain a very pale pink with hematoxylin and eosin. These bundles run almost without exception perpendicular to the epidermis (Fig. 130). The hyalin-like material surrounds all blood vessels as a thick mantle. The nuclei of the fibroblasts in the dermis and of the vascular endothelium are well preserved. In the lower dermis, the collagen appears normal, but the

homogeneous material is present around some of the vessels and sweat glands.

On staining with scarlet red, a large amount of lipid material is visualized. It stains a rusty brown and occurs in the form of small droplets throughout the hyalin-like material, but particularly around the blood vessels (Fig. 131). It is located extracellularly. On polariscopic examination, the lipid material proves to be isotropic, not doubly refractile. Urbach and Wiethe interpreted the histologic findings as indicating a merging of lipid and protein and, therefore, suggested the name lipoid proteinosis.

No definite conclusion has so far been reached about the nature of the lipid substance in the dermis. In several cases, the chemical analysis of involved skin revealed a decided increase in the amount of lecithin, which is a monoaminophosphatide (Montgomery and Havens; Ramos e Silva). In other cases, however, no such increase was found (Wile and Snow; Hansen; Price, LaRosa and Settle).

9. *Extracellular Cholesterosis (Urbach)*

This disorder is characterized by extracellular cholesterol infiltrations in the skin.

Only three cases of this condition have been reported in the literature (Urbach, Epstein and Lorenz; Laymon; Sobel and Pollock). All three cases showed reddish brown, verrucous plaques and nodules, involving especially the dorsa of the hands and the feet and the extensor surfaces of the legs. Ulceration of some of the lesions occurred in Sobel's case. The amount of cholesterol in the blood serum was normal in Laymon's case and subnormal in Urbach's and Sobel's cases.

Histopathology. The involved skin shows a dense, nonspecific, cellular infiltrate composed mainly of histiocytes and lymphocytes. The blood vessels are dilated and their endothelium is swollen. No foam cells are present. In healing lesions, there is considerable fibrosis.

Fat stains reveal numerous droplets of fat in extracellular position throughout the lesions, but especially about the blood vessels. On polariscopic examination, the fat droplets are doubly refractile.

Chemical examination of tissue in Urbach's and Sobel's cases revealed the content of cholesterol three to five times greater in the lesions than in the normal skin.

The cause of the disease is unknown. Sobel and Pollock, impressed with the subnormal values for cholesterol in their as well as in Urbach's case, suggest that, for some unknown reason, the blood is unable to hold normal amounts of cholesterol which, therefore, is

deposited in the tissue. Being unable to metabolize the cholesterol, the tissue responds not with foam cell formation but, instead, with a severe inflammatory reaction as if dealing with a foreign body of irritating or toxic nature.

LOCALIZED LIPOIDOSES

10. *Xanthelasma Palpebrarum*

This disorder is characterized by the presence of soft, yellowish plaques on the eyelids caused by the deposition of cholesterol. Although xanthelasma palpebrarum is common in primary hypercholesteremic xanthomatosis (see page 257), it frequently occurs in individuals with little or no elevation of the serum cholesterol (Epstein, Rosenman and Golman). Since, in such instances, the deposition of cholesterol probably is caused by local degenerative changes in the skin of the eyelids, xanthelasma palpebrarum is best regarded as a localized lipoidosis.

Histopathology. The histologic changes are similar to those of primary xanthomatosis. As a rule, however, fewer Touton cells are seen and they may be absent. Fibrotic changes may occur (Montgomery and Osterberg).

11. *Necrobiosis Lipoidica*

This disease represents a localized lipoidosis inasmuch as the deposition of lipids occurs in areas in which degeneration or necrobiosis of collagen has taken place. The necrobiosis of collagen is due to vascular changes (Roederer, Woringer and Burgun). In those cases in which diabetes exists, it can be assumed that the diabetes has caused the vascular changes. However, diabetes, originally thought to be a prerequisite for this disease, is present in only about one third of the cases (Kaalund-Jorgensen). In the other two thirds, the cause of the vascular changes is unknown.

Clinically, one observes on the legs, and rarely elsewhere on the skin, one or several sharply demarcated, irregularly outlined, glazed patches which are yellow in the center and violaceous at the periphery. The center gradually becomes depressed and atrophic and may break down to form an ulcer.

Histopathology. On histologic examination, the epidermis may appear normal but often is atrophic and may be absent due to ulceration of the lesion. Poorly defined areas of necrobiosis of the collagen are seen throughout the dermis, but especially in the lower portions. In these areas, the collagen appears homogeneous, swollen and partly basophilic (Fig. 132). The collagen bundles often are broken up and,

instead of lying parallel to the surface of the skin, extend in various directions. There often is evidence of formation of young collagen between the degenerated bundles.

Within and near the areas of necrobiosis, often extending into the subcutaneous fat, one finds a predominantly perivascular inflammatory infiltrate composed of lymphocytes, histiocytes, fibroblasts and

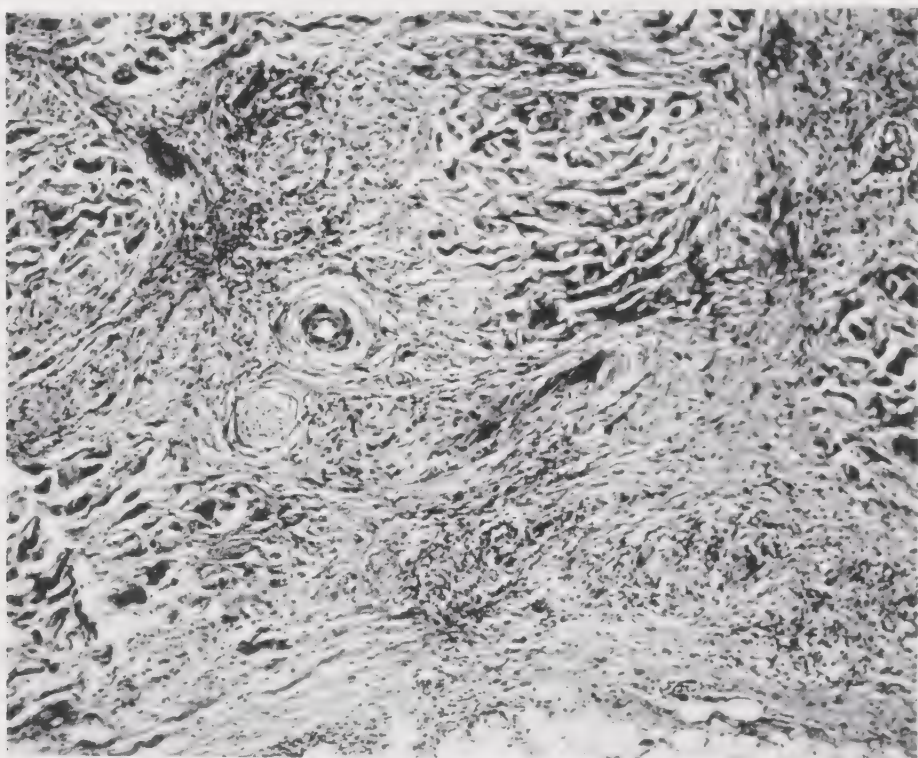


FIG. 132. *Necrobiosis lipoidica*. Much of the collagen appears degenerated. An inflammatory infiltrate is scattered through the areas of degeneration. A vessel in the center shows endothelial proliferation and fibrosis of its wall. ($\times 100$)

occasional groups of epithelioid cells. Foreign-body giant cells commonly are present and thus are of considerable diagnostic value (Michelson and Laymon; Belote and Welton) (Fig. 133). Occasionally, a few foam cells are noted (Klaber; Nicholas).

The blood vessels, particularly in the middle and the lower dermis, exhibit fibrosis of their walls with proliferation of their endothelial lining. This process may lead to partial and, occasionally, even to complete occlusion of the lumen. Thrombosis of small vessels occurs sometimes. These vascular changes account for the degeneration of the collagen.

Staining for fat with scarlet red frequently, but not always, reveals numerous granules of lipid extracellularly in the areas of collagen

degeneration. In contrast with the neutral fat in the subcutaneous layer and the sebaceous glands, which stains a brilliant orange-red, the granules stain a rusty brown. According to Hildebrand, Montgomery and Rynearson, the granules of lipids are composed of phospholipids and free cholesterol; however, the quantity of cholesterol cannot be great since the granules only rarely show double refraction

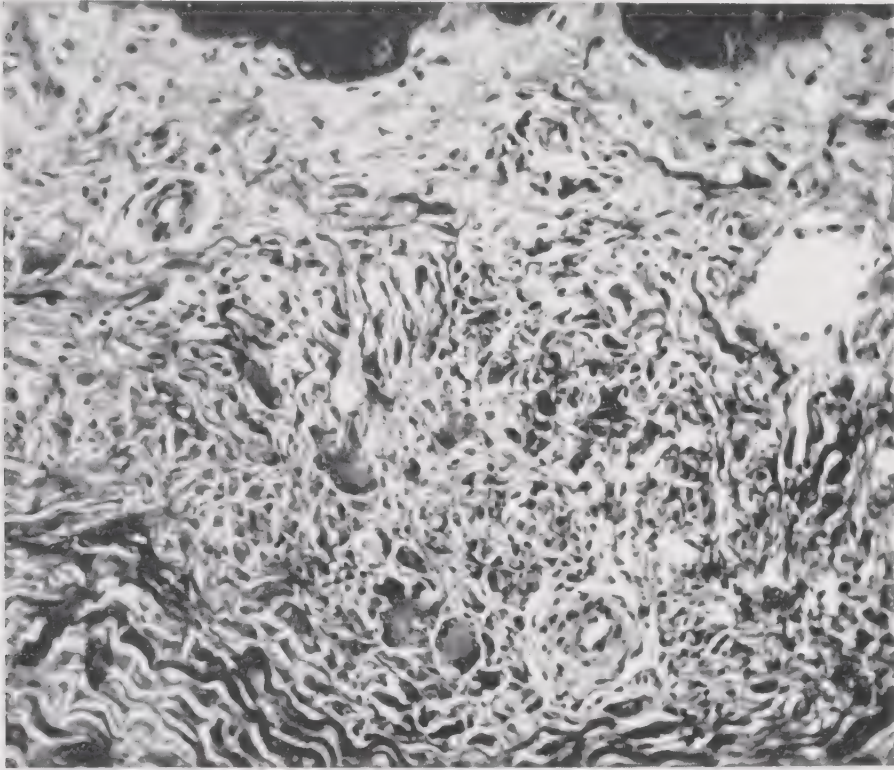


FIG. 133. *Necrobiosis lipoidica*. Several foreign-body giant cells are located within an area of collagen degeneration. Two fibrotic vessels are present. ($\times 200$)

(Laymon and Fisher). The fact that, occasionally, lipids are absent in the lesions (Sachs) indicates that their presence is purely a secondary phenomenon.

Granulomatosis disciformis chronica progressiva, recently described by several European authors (Miescher and Leder; Arzt), probably represents necrobiosis lipoidica without lipid deposits.

Differential Diagnosis. In the differential diagnosis, granuloma annulare must be considered, because both necrobiosis lipoidica and granuloma annulare show areas of collagen degeneration and the same type of reactive inflammation and fibrosis. However, in granuloma annulare there are no vascular changes, no deposits of lipids, few or no giant cells and no atrophy or ulceration of the epidermis;

on the other hand, deposits of mucin usually are present. In spite of these differences, Ellis and Kirby-Smith regard the two diseases as closely related.

AMYLOIDOSIS

Three forms of amyloidosis exist: (1) primary systemic amyloidosis, (2) primary localized amyloidosis of the skin (lichenoid amyloidosis) and (3) secondary systemic amyloidosis. In primary systemic amyloidosis, the skin is frequently involved; in secondary systemic amyloidosis, very rarely.

The Congo-red test is of great value in the diagnosis of cutaneous amyloidosis. If 1.0 cc. of a 1.5 per cent solution of Congo red is injected subcutaneously, or 0.1 cc. intradermally, into the affected region, the areas in which amyloid is deposited will be stained strongly with red dye after from 24 to 48 hours, whereas the interposed skin will appear only very slightly stained (Nomland; Dostrovsky and Sagher). In histologic sections stained with hematoxylin and eosin, amyloid appears as homogeneous, pale pink masses which contain clefts, probably because of shrinkage of the amyloid during the process of fixation. With the van Gieson stain, amyloid stains yellow and collagen red. Amyloid is a protein-polysaccharide complex and, therefore, it stains, at least in lichenoid amyloidosis and in secondary amyloidosis, red with Congo red, purple-red with methyl violet (indicating metachromasia) and deeply red with the periodic acid-Schiff reaction. In primary systemic amyloidosis, however, these staining reactions are not always present and vary from patient to patient and even from organ to organ, probably because of differences in the amount of polysaccharides or in the nature of the union between the protein and the carbohydrate molecules (Goltz).

PRIMARY SYSTEMIC AMYLOIDOSIS

Mesenchymal tissue is affected while the parenchyma of parenchymatous organs is spared. Amyloid deposits are found mainly in the smooth and striated musculature, in the small blood vessels and in the gastro-intestinal tract. Macroglossia has been present in almost one half, and cutaneous lesions in about one fourth, of the 57 cases reported up to 1949 (Dahlin).

Of interest is the frequency with which primary systemic amyloidosis is associated with multiple myeloma and Bence Jones proteinuria (Brunsting and MacDonald). Examination of the urine for Bence Jones protein, roentgenograms of the bones and sternal biopsy in search of atypical plasma cells in the bone marrow, therefore, should be performed in all cases of primary systemic amyloidosis.

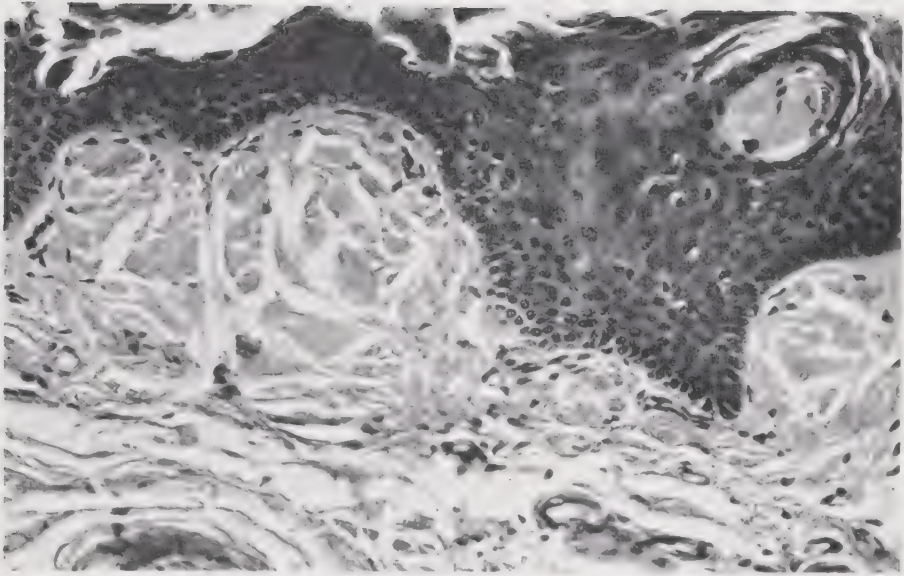


FIG. 134. Primary systemic amyloidosis. Round, amorphous, fissured masses of amyloid are present in the uppermost dermis. They resemble those of colloid milium but, in contrast to colloid milium, are present throughout the dermis. ($\times 200$)

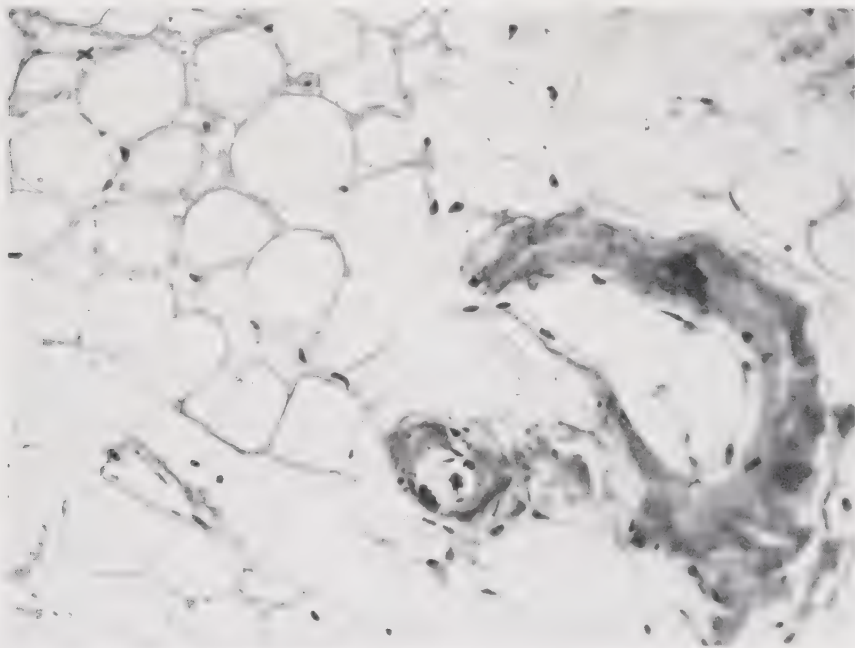


FIG. 135. Primary systemic amyloidosis. Subcutaneous fat. Amyloid is deposited in the walls of two blood vessels and also around fat cells, forming so-called amyloid rings. ($\times 400$)

Clinically, the skin shows discrete and coalescing papules and nodules which are semitranslucent and of a waxy, amber color. In addition, yellowish plaques resembling those of xanthomatosis are present. Petechiae and ecchymoses frequently occur at the site of eruption. Itching is absent. The face is predominantly affected, especially the periorbital regions.

Histopathology. Histologic examination of the skin reveals large, faintly eosinophilic, amorphous masses of amyloid which may be deposited anywhere in the dermis (Fig. 134) as well as in the subcutaneous tissue. In addition, small deposits of amyloid may occur in the membrana propria of the sweat glands, around blood vessels and in the walls of blood vessels. In most cases, no inflammatory reaction is present (Michelson and Lynch), but, in some cases, one finds foci of lymphocytes, plasma cells and foreign-body giant cells (Pearson, Rice and Dickens).

In the subcutaneous tissue, one may find, besides large masses of amyloid and deposits of amyloid in the walls of the blood vessels, so-called amyloid rings, which are formed by the deposition of amyloid around individual fat cells (Fig. 135) (Pearson, Rice and Dickens). The fat cells thus appear as if cemented together by the eosinophilic amyloid substance (Iverson and Morrison).

Not only in the skin and the subcutaneous tissue, but also throughout the body, the small arteries and the veins show amyloid deposits, often entirely replacing their media and adventitia. The vessels of the tongue, the skeletal muscle, the respiratory tract, the heart and the gastro-intestinal and the genito-urinary tracts usually are affected most severely. In the skeletal muscle and in the tongue, numerous muscle fibers show amyloid deposits in the form of amorphous nodular swellings (Iverson and Morrison).

PRIMARY LOCALIZED AMYLOIDOSIS OF THE SKIN (LICHENOID AMYLOIDOSIS)

In this form of amyloidosis, only the skin is involved. The lesions are seen most commonly on the legs but they may occur elsewhere. They consist of closely set, discrete, conical or flat, brownish red papules which resemble the papules of lichen planus. Occasionally, the papules have a translucent appearance. In some instances, the papules, by coalescence, form plaques which may develop a verrucous surface and then resemble lichen simplex chronicus. The lesions usually itch severely in contrast with those of primary systemic amyloidosis.

Histopathology. The amyloid deposits are much smaller in size than those found in primary systemic amyloidosis and are limited to the subepidermal region of the dermis. The earliest deposits occur

about capillaries (Nomland). In some cases, a mild chronic inflammatory infiltrate will be found.

Differential Diagnosis. Lichenoid amyloidosis must be differentiated from colloid milium. For differential diagnosis, see page 165.

SECONDARY SYSTEMIC AMYLOIDOSIS

This condition occurs in chronic suppurative diseases, such as tuberculosis, and in chronic cachectic diseases associated with marked loss of protein from the body. Amyloid deposits are found in the parenchymatous organs, especially in the liver, the kidney, the spleen ("sago spleen") and the adrenals. The skin is involved very rarely. Michelson and Lynch have reported a case of secondary systemic amyloidosis due to tuberculosis in which there were diffuse nodular lesions of the lips due to deposits of amyloid.

CALCINOSIS CUTIS

Two forms of calcinosis cutis exist: metastatic and metabolic calcification.

METASTATIC CALCIFICATION

Metastatic calcification develops as a result of hypercalcemia. The hypercalcemia may be due to parathyroid neoplasm, hypervitaminosis D, chronic renal disease or destruction of bone in such conditions as osteomyelitis and malignant growths (Mulligan). Calcium is apt to be deposited in organs in which the cells excrete acid and therefore have a low carbon dioxide tension. As a result of the low carbon dioxide tension, calcium becomes less soluble and precipitates.

Metastatic calcification occurs mainly in the kidneys, the lungs and the stomach since the cells of these organs excrete acid substances. The skin and the subcutaneous tissue are affected only rarely. However, instances of metastatic calcification of either skin or subcutaneous tissue have been reported as caused by parathyroid neoplasm (Penecke; Laubmann), by hypervitaminosis D (Bevans and Taylor), by chronic renal disease (Platt and Owen) and by osteomyelitis (Weidman and Shaffer).

Histopathology. Calcium deposits are recognized easily in histologic sections since they stain deeply blue with hematoxylin and eosin, and black with von Kossa's stain for calcium. In most instances of metastatic calcification, the calcium occurs as individual granules as well as massive deposits in the dermis and in the subcutaneous fat (Fig. 136). Larger deposits often evoke a foreign-body reaction so that giant cells, an inflammatory infiltrate and fibrosis may be present around them. In Weidman and Shaffer's case, the calcium deposits consisted of small granules which were found not only in the

dermis but also in the epidermis, in the sweat glands, in the sweat ducts and in the nerve trunks.

METABOLIC CALCIFICATION

Metabolic calcification is due to local metabolic disturbances and is not associated with hypercalcemia. Deposits of calcium occur, as a rule, only in the skin and the subcutaneous tissue, but occasionally

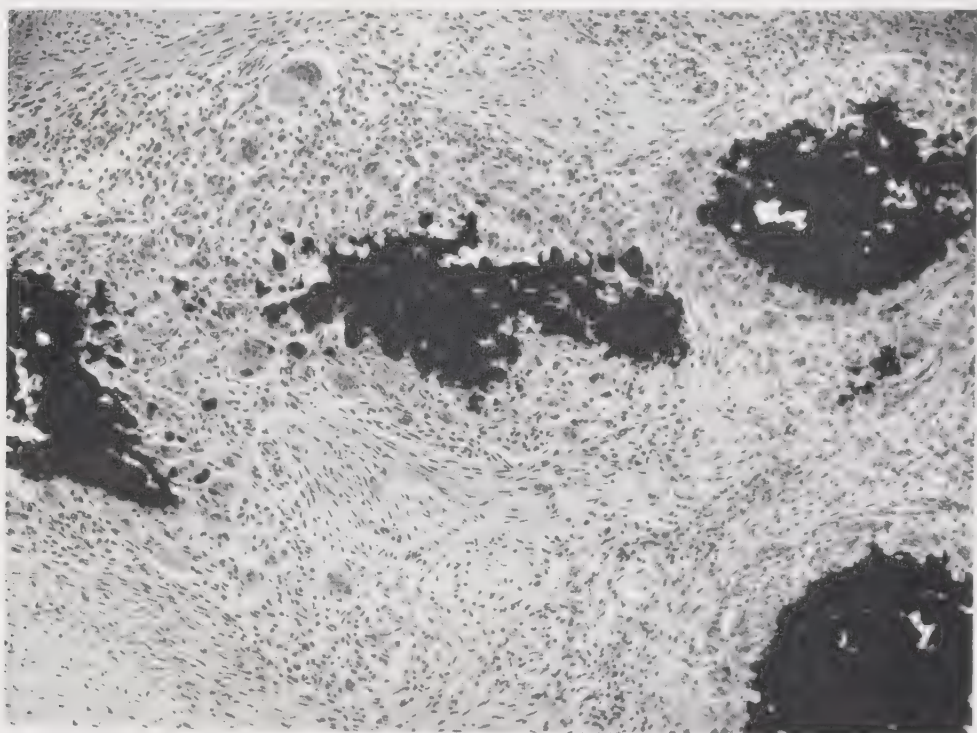


FIG. 136. Metastatic calcification as a result of hypercalcemia (produced by prolonged and excessive administration of vitamin D). Von Kossa stain for calcium. Irregular masses of calcium surrounded by a foreign-body giant cell reaction are present in the subcutaneous fat. ($\times 100$)

also in the muscles and the tendons. The internal organs are spared. There may be just a few deposits (calcinosis circumscripta) or innumerable deposits everywhere in the skin (calcinosis universalis). Between 30 and 40 per cent of the cases of calcinosis circumscripta and universalis described in the literature occurred in patients with scleroderma or dermatomyositis (Atkinson and Weber). (See "Scleroderma," page 310, and "Dermatomyositis," page 303.) In the rest, no reason for the calcinosis was evident.

Histopathology. As in metastatic calcification, the calcium may be present as individual granules or as massive deposits in the dermis and in the subcutaneous fat. In the subcutaneous fat, extensive areas of calcification may be observed. A foreign-body giant-cell reaction is often found around the larger deposits of calcium.

In sclerodermic calcinosis, the histologic appearance of the skin and the subcutaneous tissue is that of scleroderma. The calcium deposits are usually located within areas of sclerotic collagen. The deposition of calcium probably is due to the decreased metabolic activity in the sclerotic tissue. Decreased metabolic activity causes the carbon dioxide tension in the tissue to be lower than normal and thus reduces the solubility of calcium (Brody and Bellin).

In patients with idiopathic calcinosis cutis, no perceptible histologic changes may precede the deposition of the calcium (Epstein; Bauer, Marble and Bennett). Bauer, Marble and Bennett found, in their case, that the initial lesion consisted of deposition of finely divided particles of calcium salts around apparently normal fat cells in the subcutaneous tissue. The granules seemed to coalesce slowly to form large masses. Other authors found that, even in idiopathic calcinosis, mild degenerative changes preceded the deposition of calcium (Rothstein and Welt; Atkinson and Weber).

GOUT

Gout is a disturbance of purine metabolism characterized by arthritis. Deposits of urates are found in the tissues of the joints, particularly their cartilages, in the cartilage of the ears and in the

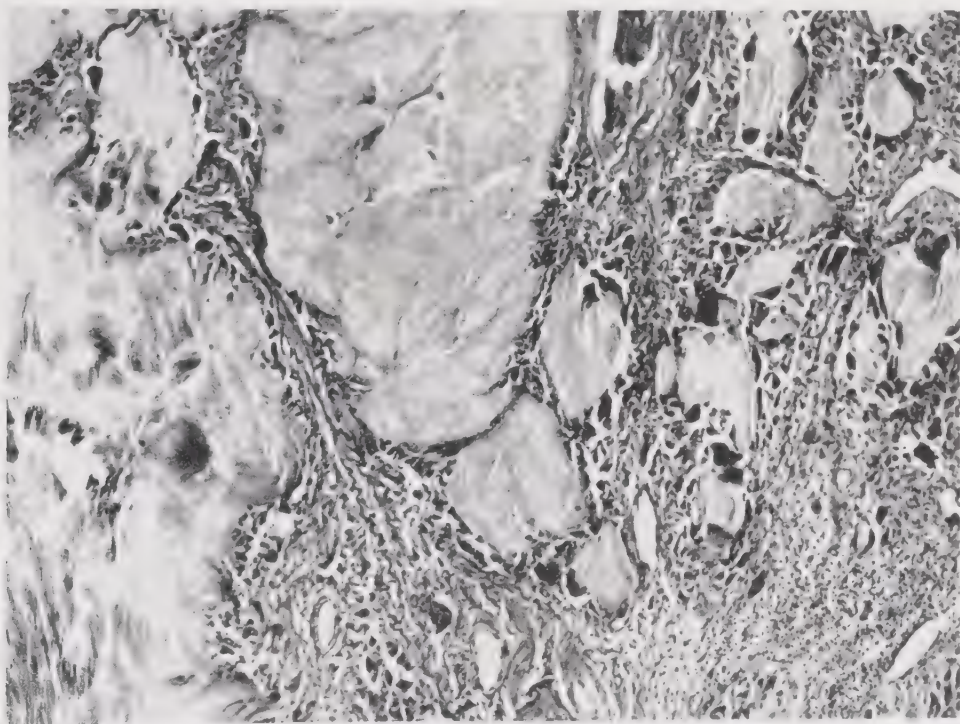


FIG. 137. Gout. Deposits of sodium biurate are surrounded by a foreign-body giant-cell reaction. On the left, the sodium biurate is present as needle-shaped crystals. ($\times 100$)

subcutaneous tissue. The deposits in the ears and in the skin manifest themselves as nodules of varying size. These nodules are called tophi.

Histopathology. The tophi show needle-shaped crystals of sodium biurate lying closely packed in the form of bundles or sheaves. The crystals often have a brownish color. They stain well with von Kossa's stain. The accumulations of urates are surrounded by granulation tissue containing many foreign-body giant cells (Fig. 137).

PORPHYRIA

Porphyria represents an inborn metabolic error in which large amounts of uroporphyrin and coproporphyrin are excreted in the urine. Three forms of porphyria exist: the congenital form, the acute intermittent form and the delayed cutaneous form. In the congenital form, the porphyrins are formed in the bone marrow (porphyria erythropoietica), while in the acute intermittent form and in the delayed cutaneous form they are formed in the liver (porphyria hepatica) (Watson).

In the congenital form, cutaneous lesions identical with those seen in hydroa vacciniforme appear from earliest childhood on the exposed portions of the skin following exposure to the sun. The lesions result in scarring and mutilation. The teeth may appear red.

The acute intermittent form starts in adult life and is characterized by attacks of abdominal pain, peripheral neuropathy and mental disturbances. Cutaneous lesions do not occur, as a rule. However, in rare instances, cutaneous lesions like those in the delayed, cutaneous form have been observed (Nesbitt and Watkins).

The delayed cutaneous form (porphyria cutanea tarda), like the acute intermittent form, remains latent until adult life. Frequently, chronic alcoholism by causing hepatic dysfunction precipitates the onset of clinical manifestations. Blisters form on exposure to light as well as on minor mechanical or thermal trauma. They often heal with scarring and formation of milia. Abdominal pain and nervous-system manifestations, as in the acute intermittent type, may be present, although to a lesser degree (Brunsting and Mason). Because of the occurrence of blisters following trauma and the presence of milia, some authors have referred to the lesions as acquired epidermolysis bullosa. However, the excretion of uroporphyrin and coproporphyrin in the urine and the presence of sensitivity to light make it evident that the disease is not related to epidermolysis bullosa (Brunsting and Mason).

Histopathology. In the congenital form, the vesicles have the same appearance as in hydroa vacciniforme (see page 46).

In the delayed cutaneous form, the bullae arise as "pressure bullae" (see page 66) subepidermally (Zeligman and Baum; Robert). However, due to regeneration of the epidermis, older bullae may be located partially or entirely within the epidermis. The bullae, thus, do not differ histologically from those observed in epidermolysis bullosa. The milia, like those of epidermolysis bullosa dystrophica, consist of small, intradermally located epidermal cysts (Robert).

MYXEDEMA

Three types of myxedema occur: generalized myxedema, circumscribed myxedema and papular myxedema. Generalized myxedema is a manifestation of hypothyroidism. Circumscribed myxedema is associated with or preceded by hyperthyroidism and occurs almost invariably together with exophthalmos; commonly, it follows thyroidectomy or therapy with thiouracil. Papular myxedema is not associated with any disturbance of thyroid function.

The mucin present in the tissue in these three diseases appears light blue on staining with hematoxylin and eosin. It stains red with the periodic acid-Schiff reaction and is strongly metachromatic with methylene blue, thionine, cresyl violet and toluidene blue, indicating that it is a protein-polysaccharide complex (Brewer). The mucin is digested in sections by hyaluronidase, which points to the fact that it contains a large amount of hyaluronic acid (Palitz and Brunner). It also stains red with mucicarmine. (The latter staining method requires fixation with absolute alcohol—see page 29.)

GENERALIZED MYXEDEMA

Clinically, the entire skin appears swollen, dry, pale and waxy. It feels firm to the touch. In spite of its edematous appearance, the skin does not pit on pressure. The facies is characteristic: the nose is broad and thick and the lips are swollen.

Histopathology. The dermis is increased in thickness. The collagen bundles as well as the individual fibers of the collagen bundles are separated by edema. The collagenous fibers show signs of degeneration, such as swelling and fragmentation. In the interstices between collagen fibers and collagen bundles, fine, bluish threads and granules of mucin are seen. The amount of mucin is usually small (Reuter).

CIRCUMSCRIBED MYXEDEMA

The lesions usually are limited to the anterior aspects of the legs. They consist of hard, raised, nodular, yellow, waxy plaques with prominent hair follicles.

Histopathology. Large amounts of mucin are present in the dermis, particularly in the lower dermis. There it occurs not only as individual threads and granules, but also as massive deposits causing wide separation of the collagenous fibers (Fig. 138). The number of

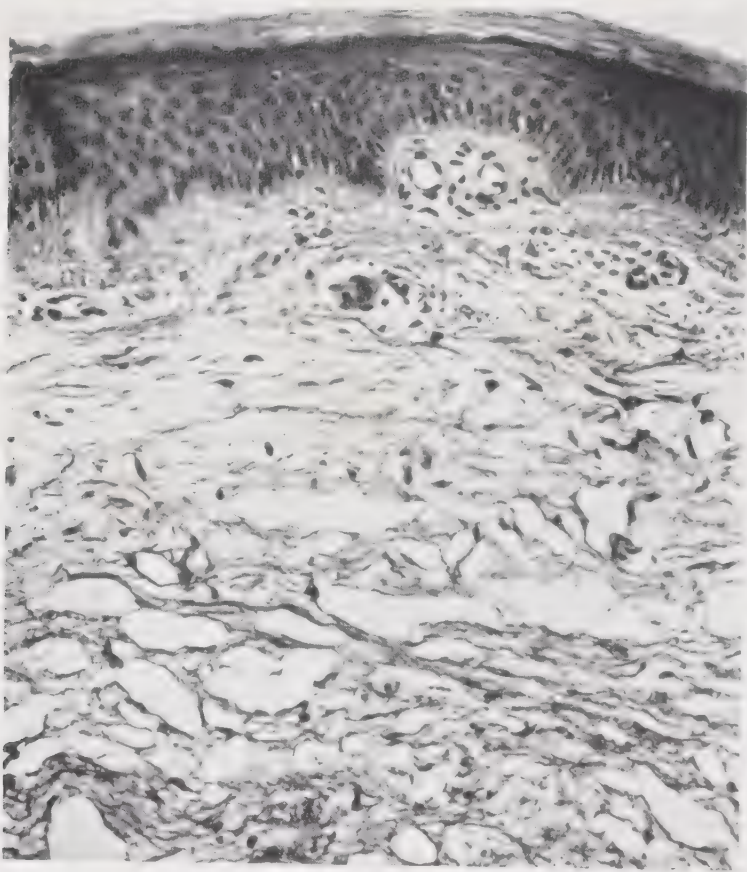


FIG. 138. **Circumscribed myxedema.** Considerable amounts of mucin are present, especially in the lower dermis, separating the collagen bundles as well as individual collagen fibers. (The empty spaces are due to shrinkage and falling out of mucin.) ($\times 200$)

fibroblasts is increased and newly formed collagen is present. Some fibroblasts have a stellate shape and are surrounded by mucin. Because of the much larger amount of mucin and the new formation of collagen, the dermis is greatly thickened, much more than in generalized myxedema.

The epidermis shows hyperkeratosis. The rete ridges are often flattened. The vessels in the upper dermis are dilated and surrounded by a mild inflammatory infiltrate. Elastic tissue stains show the elastic tissue to be frayed and greatly decreased (O'Leary).

PAPULAR MYXEDEMA (PAPULAR MUCINOSIS)

There is a widespread eruption of asymptomatic, soft, yellowish papules which may coalesce into irregular patches.

Histopathology. The appearance of the mucinous infiltrate is like that in circumscribed myxedema inasmuch as there are rather large amounts of mucin as well as stellate cells (Dalton and Seidell). However, the extent of the mucinous infiltrate is more limited than in circumscribed myxedema because it is present only in the upper dermis and, in the case of individual papules, within relatively small areas.

SCLEREDEMA ADULTORUM (BUSCHKE)

Scleredema adultorum is characterized by diffuse edema and induration of the skin and the subcutaneous tissue. Its cause is unknown but it is noteworthy that it frequently follows an infectious disease such as grippe or tonsillitis. It usually begins on the face and spreads rapidly to involve the neck and the upper trunk. Complete resolution takes place in a few months. The occurrence of pleural and pericardial effusions and of hydrarthrosis has been reported (Vallee).

Histopathology. Throughout the dermis, one observes swelling and splitting up of the collagen bundles by edema. The edema may be severe enough to produce in the dermis clear, unstained spaces of various sizes ("fenestration"). Freund noted that the edema substance, which did not stain with hematoxylin and eosin, stained metachromatically with cresyl violet, like mucin, but not with mucicarmine. Vallee found this staining reaction in one case but not in another. Braun-Falco observed purplish metachromasia with toluidene blue which was no longer present when the sections, prior to the staining, were incubated with hyaluronidase. He concluded that the edema substance consisted of hyaluronic acid.

ADDISON'S DISEASE

Addison's disease, which is caused by hypofunction of the adrenal glands, is characterized by weakness, loss of weight, low blood pressure and diffuse hyperpigmentation of the skin and the mucous membranes.

The hyperpigmentation in Addison's disease is the result of an excessive production of the hormone intermedin in the intermediary lobe of the pituitary gland (Hall, McCracken and Thorn). The reason for this excessive production is that, in Addison's disease, the damaged adrenal gland responds but weakly to pituitary stimulation and,

consequently, as a compensatory phenomenon, the pituitary gland is overactive.

Histopathology. Histologic examination often shows no changes other than hyperpigmentation. Occasionally, one observes slight flattening of the rete ridges and slight thinning of the epidermis. The amount of melanin is increased in both the epidermis and the dermis. In the epidermis, the melanin is present chiefly in the basal layer, but may be found also in the lower layers of the stratum malpighii. Because the pigment formation proceeds slowly over a long period of time, the number of clear cells is increased only slightly. In the upper dermis, a moderate number of melanin-laden chromatophores (melanophores) are present. There is no inflammatory reaction in the dermis.

Differential Diagnosis. A diagnosis of Addison's disease cannot be made from histologic sections, because the same histologic picture is observed in nonspecific hyperpigmentation of the skin and in the normal skin of the Negro.

ACANTHOSIS NIGRICANS

Three types of acanthosis nigricans exist: malignant acanthosis nigricans, benign acanthosis nigricans and pseudo-acanthosis nigricans. Clinically and histologically, the three forms look alike (Curth).

The malignant form occurs in adults and is associated with internal cancer, usually of the glandular type. The benign or juvenile form may start at any time before puberty. It represents a genodermatosis related to nevus verrucosus. Pseudo-acanthosis nigricans occurs in the body creases of obese, brunette persons. It disappears when the patient loses weight.

Clinically, all three forms of acanthosis nigricans present verrucous, hyperpigmented patches, predominantly in the axillae, on the neck and in the submammary and the genital regions.

Histopathology. Histologic examination reveals marked hyperkeratosis and papillomatosis. In addition, acanthosis and hyperpigmentation are present but are slight (Fig. 139). Thus, the name acanthosis nigricans has little histologic justification.

In a typical lesion, the papillae project far upward as finger-like projections and are covered with a not unduly thickened stratum malpighii. The valleys between the finger-like projections are filled in largely by keratin. In areas where there is no papillomatosis, the epidermis shows areas of moderate acanthosis with adjacent areas of atrophy of the stratum malpighii. The rete ridges, as a rule, are developed only poorly. There may be a slight increase in the amount of melanin in the basal layer.

Differential Diagnosis. Differentiation of *acanthosis nigricans* from *nevus verrucosus* may be impossible (Curth). As a rule, however, *nevus verrucosus* shows more marked acanthosis than *acanthosis nigricans* and overdevelopment rather than atrophy of the rete ridges.

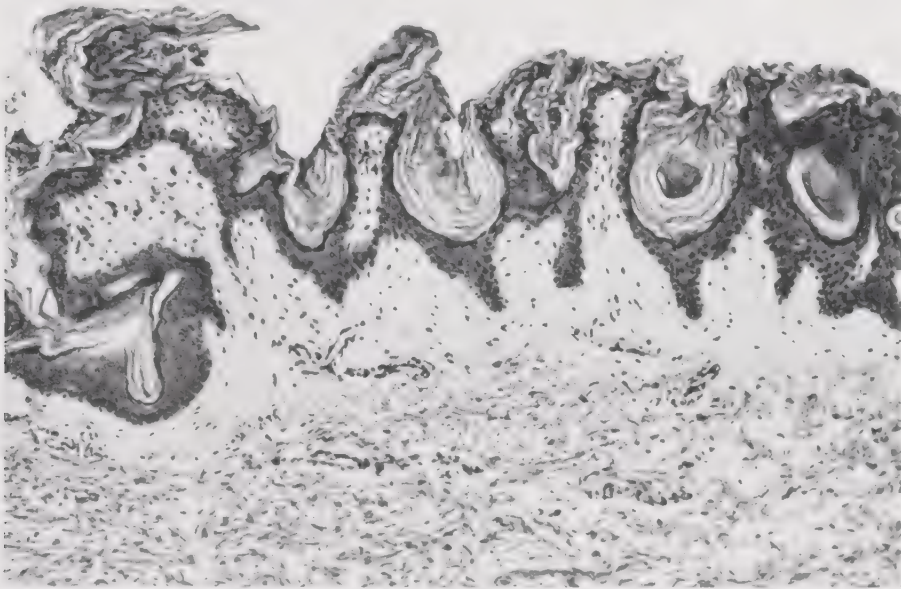


FIG. 139. *Acanthosis nigricans*. There are hyperkeratosis and papillomatosis. Several papillae project upward as finger-like projections. As is usually the case, acanthosis and hyperpigmentation are slight. ($\times 100$)

RIEHL'S MELANOSIS. MELANODERMATITIS TOXICA. POIKILODERMA RETICULARE (CIVATTE)

Riehl's melanosis and melanodermatitis toxica have the same appearance clinically as well as histologically (Storck). In both conditions, one observes ill-defined, symmetrical, bluish brown hyperpigmentation of the face and, occasionally, also of the neck and the chest. There may be slight atrophy of the skin and follicular hyperkeratosis. The cause of Riehl's dermatosis is not fully known, but it has been suggested that it is caused by a lack of vitamin B and provoked by exposure to the sun, and that thus it is related to pellagra (Poehlmann). Melanodermatitis toxica is due to contact of the affected skin with tars, oils or greases.

Poikiloderma reticulare differs from these two diseases clinically by its predominant localization on the neck, the reticular arrangement of the hyperpigmentation and the presence of telangiectases (Pierini and Bosq). Histologically, the telangiectases usually are not sufficiently evident to differentiate poikiloderma reticulare from the other two diseases.

Histopathology. The clinically visible hyperpigmentation in these three diseases is brought about by pigmentary incontinence of the basal layer, resulting in an accumulation of melanin in the upper dermis. The epidermis shows mild hyperkeratosis, thinning of the stratum malpighii and varying degrees of degeneration of the cells in the basal layer. The amount of melanin in the basal layer is decreased. The papillary and the subpapillary layers of the dermis, how-

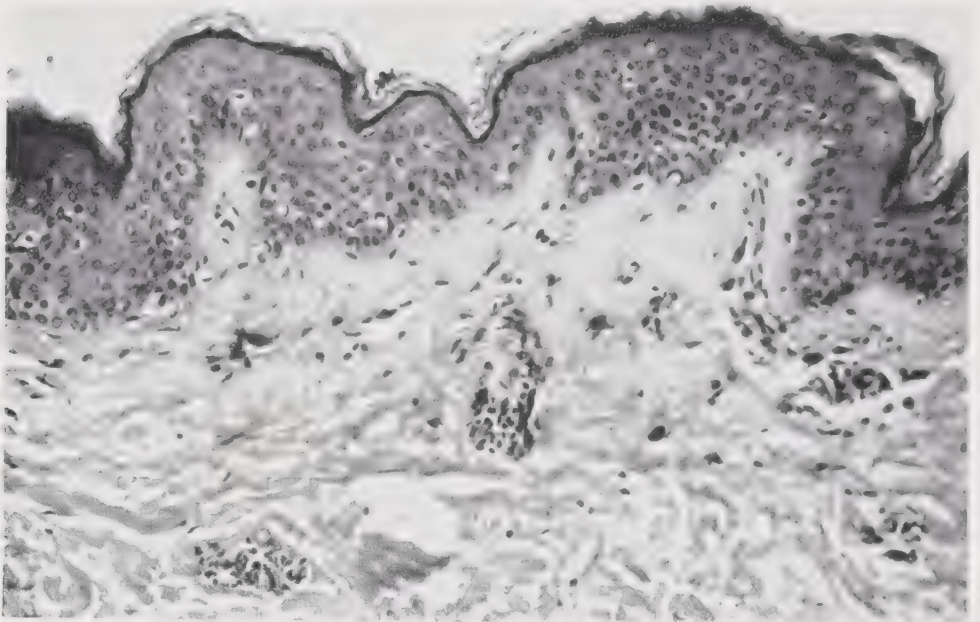


FIG. 140. **Melanodermatitis toxica.** The basal layer shows numerous clear cells. The upper dermis shows large amounts of melanin, mainly within but also outside of chromatophores. A mild perivascular inflammatory infiltrate is present. ($\times 200$)

ever, show large amounts of melanin, mainly within, but also outside of, chromatophores (Fig. 140). In addition, there are various degrees of inflammatory reaction in the upper dermis. In some cases, the inflammatory infiltrate is limited to the perivascular areas; in others, it is extensive, bandlike and close to the epidermis, and thus resembles that of lichen planus (Storck).

At a later stage, the degeneration of the basal layer is slight and many clear cells may be present. The degree of inflammation lessens with the age of the lesion.

Differential Diagnosis. Incontinentia pigmenti differs from the three diseases just discussed by showing no inflammatory infiltrate in the upper dermis. Addison's disease shows no inflammatory infiltrate either and only a slight amount of melanin in the dermis.

VITILIGO

Vitiligo is characterized by variously sized and shaped, sharply demarcated patches of depigmentation surrounded by hyperpigmented skin.

Histopathology. In the depigmented areas, the epidermis is devoid of pigment. It is otherwise unchanged. Even melanocytes (clear cells of Masson) are still present (Becker). The upper dermis may contain a few melanophores. In the adjoining hyperpigmented skin, the amount of melanin in the basal layer is increased and numerous melanophores are present in the upper dermis.

The dopa reaction is negative in the basal layer of the depigmented areas and positive in the basal layer of the adjoining hyperpigmented areas.

HEMOCHROMATOSIS (BRONZE DIABETES)

This disturbance of the metabolism is characterized by deposition of hemosiderin in various organs of the body. The presence of hemosiderin causes "bronzing" of the skin, cirrhosis of the liver and sclerosis of the spleen and the pancreas. Sclerosis of the pancreas is responsible for the diabetes usually associated with the disease.

Clinically, the pigmentation of the skin is diffuse and is indistinguishable from that seen in Addison's disease.

Histopathology. Granules of hemosiderin are found within chromatophores in the upper dermis and in the membrana propria of the sweat glands. Occasionally, they may also occur in the basal cells of the epidermis. Hemosiderin is best demonstrated by staining sections with potassium ferrocyanide. With this method, hemosiderin granules, on account of their content of iron, stain blue. Not infrequently, melanin is present in excess in the basal layer and within chromatophores.

In selecting a site for biopsy, it is not necessary to choose a pigmented area, because hemosiderin is present throughout the skin in hemosiderosis. However, it is important not to take a specimen from the legs, where deposits of hemosiderin frequently occur in association with stasis dermatitis and other vascular disturbances (Montgomery and O'Leary).

Differential Diagnosis. It is impossible to differentiate the granules of hemosiderin from those of melanin in routine stains. They can, however, be easily differentiated by staining with potassium ferrocyanide, which stains hemosiderin blue but does not stain melanin. Furthermore, melanin does not occur in the membrana propria of the sweat glands.

The granules of silver, present in argyria, are also frequently located in the membrana propria of the sweat glands, but they differ from those of hemosiderin by being much smaller and more uniform in size. Furthermore, they do not stain with potassium ferrocyanide and are refractile with dark-field illumination (see page 153).

OCHRONOSIS

In ochronosis, due to an inborn metabolic error, the catabolism of tyrosine cannot proceed beyond homogentisic acid. The disease is characterized by blackening of the cartilages and by osteo-arthritis and may show bluish discoloration of the sclerae and brown or bluish mottled pigmentation of the skin. The urine darkens on exposure to the air. The discoloration of the cartilages, the sclerae and the skin, as well as the darkening of the urine, are due to the presence of homogentisic acid which by oxidation is converted into a dark-colored insoluble product.

Histopathology. Varying amounts of a light brown pigment are present in the dermis. The pigment is either diffusely distributed or present as clumps of varying size and shape. The clumps may be large, measuring more than 100 microns in diameter. The pigment does not stain with silver nitrate as melanin does but becomes black when stained with polychrome methylene blue (Laymon).

VITAMIN A DEFICIENCY (PHRYNODERMA)

Vitamin A plays an important part in the metabolism of the epithelial structures of the skin and the mucous membranes. In addition to cutaneous changes, deficiency of vitamin A may cause night blindness, xerophthalmia and keratomalacia.

The cutaneous changes, to which the name phrynoderma has been given, consist of dryness and roughness of the skin and the presence of follicular hyperkeratosis.

Lichen spinulosus of Crocker is probably identical with phrynoderma (Lehman and Rapaport).

Histopathology. The skin shows moderate hyperkeratosis with marked distention of the upper part of the hair follicles by large horny plugs. In contrast with ichthyosis, the granular layer is present and may even be increased in thickness. The lower part of the hair follicles is atrophic and usually surrounded by a slight, chronic inflammatory infiltrate. There are only few remnants of sebaceous glands. In addition, one may find evidence of atrophy of the sweat glands, such as flattening of the secretory cells (Frazier and Hu). In severe cases, the sweat glands and the sebaceous glands may undergo keratinizing metaplasia (Bessey and Wolbach). When adequate amounts of vitamin A are supplied to a patient with phrynoderma,

there may be considerable regeneration of the cutaneous appendages (Steffens, Bair and Sheard).

Differential Diagnosis. Differentiation of phrynoderma from ichthyosis may be difficult. As a rule, however, ichthyosis shows atrophy or absence of the granular layer, thinning of the epidermis and elongation and branching of the rete ridges. Pityriasis rubra pilaris differs from phrynoderma by showing, in addition to hyperkeratosis and follicular plugging, spotted parakeratosis, irregular acanthosis and a more pronounced inflammatory infiltrate, not limited to the hair follicles.

PELLAGRA

Pellagra is caused by a deficiency of the vitamin B complex but particularly of nicotinic acid. Besides cutaneous lesions, pellagra usually presents also a stomatitis, which is characterized by edema and redness of the tongue and atrophy of the lingual papillae. In addition, gastro-intestinal symptoms and nervous and mental changes may be present.

Cutaneous lesions occur predominantly on exposed areas, such as the dorsa of the hands, the wrists, the face, the V-area of the upper chest and the dorsa of the feet. In the early stage, there is erythema, which in severe cases may be accompanied by bullae. Later, the erythema assumes a livid shade and the skin becomes thickened and scaling. Ultimately, the affected areas become atrophic and deeply pigmented.

Histopathology. Early lesions present a chronic inflammatory infiltrate with moderate edema in the upper dermis. Vesicles and bullae may be present. They may be located intra-epidermally as well as subepidermally.

Older lesions show hyperkeratosis with areas of parakeratosis and a moderate degree of acanthosis. Follicular plugging occasionally is observed. The amount of melanin in the epidermis is increased. The dermis shows edema, swelling of the collagen fibers and a chronic inflammatory infiltrate. Severe cases may show, in addition, hyalinization and mucoid degeneration of the collagenous fibers in the deeper portions of the dermis (Moore, Spies and Cooper).

In the end stage, hyperkeratosis and hyperpigmentation are still present, but the stratum malpighii now shows considerable atrophy with flattening of the rete ridges. The dermis shows moderate fibrosis.

Differential Diagnosis. The histologic picture of pellagra is not diagnostic. As a rule, it is merely one of chronic dermatitis. In the end stage, the presence of hyperpigmentation and of atrophy of the stratum malpighii serves to distinguish pellagra from chronic dermatitis.

VITAMIN C DEFICIENCY (SCURVY)

Scurvy, caused by a deficiency of ascorbic acid, is characterized by bleeding and spongy gums and petechial hemorrhages which often are perifollicular.

Histopathology. Scurvy is characterized by inability of the supporting tissues to produce and maintain intercellular substances (Wolbach and Howe). Thus, the endothelial cells of capillaries fail to form adequate amounts of intercellular ground substance. Extravasation of red blood cells results. The extravasation occurs without inflammatory changes around the capillaries. Scurvy, consequently, belongs to the group of noninflammatory purpuras (see page 127) (Peck, Rosenthal and Erf).

Histologic examination of the skin shows hemorrhages around the capillaries. As a rule, these hemorrhages are most pronounced in the vicinity of the hair follicles. In many instances, one finds hyperkeratosis and follicular plugging, as in vitamin A deficiency. According to Scheer and Keil, these changes in the epidermis are purely secondary.

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17

Systemic Diseases of Unknown Cause

LUPUS ERYTHEMATOSUS

Three types of lupus erythematosus are generally recognized: (1) chronic discoid lupus erythematosus, (2) subacute disseminate lupus erythematosus and (3) acute systemic lupus erythematosus. In the first type, the lesions are limited to the skin. In the second type, systemic symptoms may occur. In the third type, visceral lesions dominate the picture and cutaneous lesions may be absent. Intermediary forms between the three types occur, clinically as well as histologically. They cannot be regarded as separate diseases.

Clinical Appearance. Chronic discoid lupus erythematosus is limited usually to the face, where the flush areas of the cheeks are affected predominantly. The scalp and the ears also may be involved. The lesions consist of well-defined, erythematous, slightly infiltrated patches showing adherent, keratotic scaling and follicular plugging. Older lesions show, in addition, atrophic scarring. Systemic symptoms are absent.

Subacute disseminate lupus erythematosus usually is superimposed upon chronic discoid lupus erythematosus but may begin as such. In addition to the face, other areas, especially the thorax and the arms and the legs, are involved. Systemic symptoms, such as fever, malaise and leukopenia, are often present. The lesions consist of erythematous, often slightly livid, patches which tend to coalesce and show only slight scaling. The prognosis as to life is fairly good, since development into the fatal acute form of the disease is not common.

Acute systemic lupus erythematosus has severe systemic symptoms and almost invariably is fatal. Even corticotropin and cortisone, as a rule, merely delay death because the renal lesions do not respond to these drugs. Systemic symptoms often precede the cutaneous eruption and, occasionally, cutaneous manifestations are absent throughout the course of the disease. The cutaneous eruption frequently begins on the face as a diffuse, ill-defined erythema with some edema

("erythema perstans"). Soon other lesions appear, often widely spread over the body. They are poorly defined, purplish and often edematous, and may be purpuric or vesicular. The systemic symptoms include irregular fever, malaise, weakness, pains in muscles and joints and pleural pain. Laboratory findings include marked leukopenia, hypergammaglobulinemia, proteinuria and often hematuria.

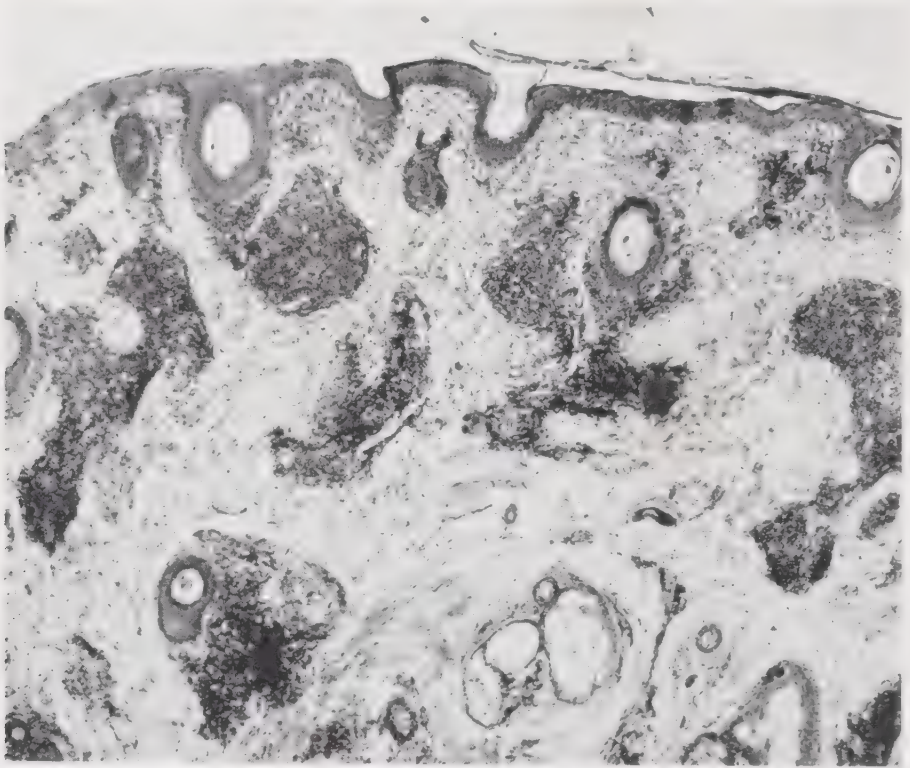


FIG. 141. Chronic discoid lupus erythematosus. Low magnification. There is keratotic plugging and the follicles inside the dermis contain, instead of hairs, concentric layers of keratin. The epidermis is atrophic and devoid of rete ridges. The inflammatory infiltrate is distinctly patchy and tends to be located in the vicinity of hair follicles. ($\times 50$)

Histopathology of Chronic Discoid Lupus Erythematosus. In most instances, a histologic diagnosis is possible on the basis of a combination of pathologic findings. There are five cardinal changes in the skin: (1) hyperkeratosis with keratotic plugging; (2) atrophy of the stratum malpighii; (3) liquefaction degeneration of the basal cells; (4) a patchy, perivascular, chiefly lymphocytic infiltrate with a tendency to arrangement about the dermal appendages and (5) basophilic degeneration of the collagen (Fig. 141). However, not all five changes are present in every case.

The epidermal changes are secondary to those in the dermis. There-

fore, the hyperkeratosis may not be present until after the lesion is several weeks old. Parakeratosis is usually completely absent. The keratotic plugs are found mainly in the follicular openings but occur also in the sweat ducts and independent of either. The follicles inside the dermis may contain concentric layers of keratin instead of hairs (Fig. 141). The atrophy of the stratum malpighii is not always uni-

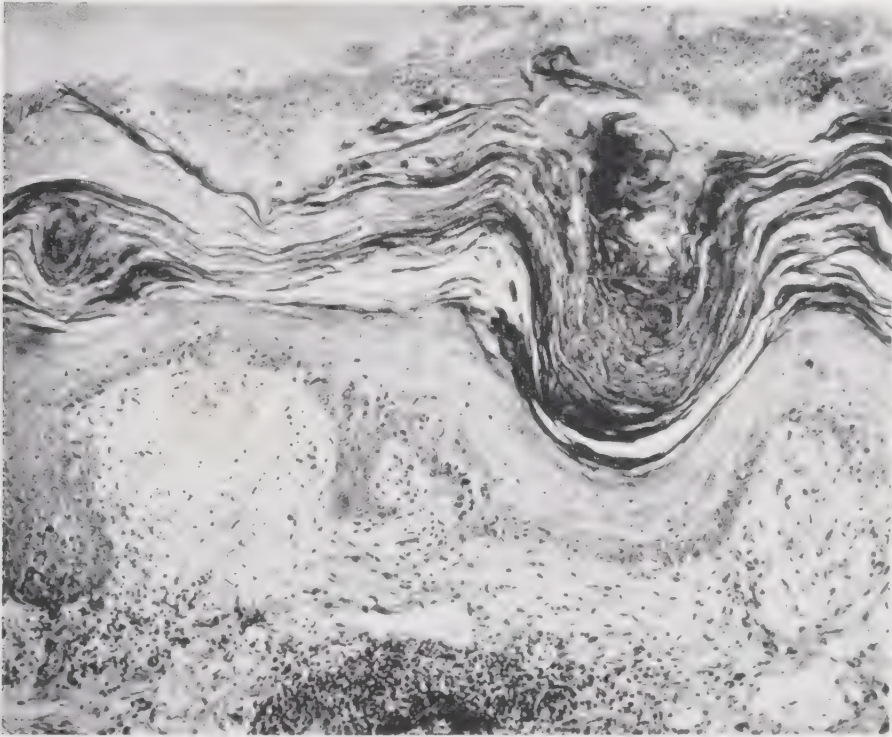


FIG. 142. Chronic discoid lupus erythematosus. High magnification. There are keratotic plugging, atrophy of the epidermis, liquefaction degeneration of the basal layer, edema of the upper dermis with basophilic degeneration of the collagen and a patchy, predominantly lymphocytic infiltrate. ($\times 200$)

form but may alternate with areas of acanthosis. Focal liquefaction degeneration of the basal layer represents the most significant histologic change in lupus erythematosus (Fig. 142). In its absence, a histologic diagnosis of lupus erythematosus is rarely, if ever, justified. In older lesions, the basal layer often is partially absent as a consequence of this degeneration.

The dermis shows considerable edema in its upper portion. In darkly skinned persons, melanin is often present in the upper dermis since the degeneration of the cells in the basal layer causes them to lose their melanin ("pigmentary incontinence"). The capillaries and larger vessels are dilated and their walls may show edema; however,

proliferative or obliterative changes are absent. The inflammatory infiltrate is distinctly patchy. It is located mainly in the vicinity of the hair follicles and the sebaceous glands, presses upon these structures and causes their gradual atrophy and disappearance (Fig. 141). The infiltrate is composed predominantly of lymphocytes but contains also a small number of plasma cells and histiocytes.

Basophilic degeneration of the collagen in the upper dermis is common in sections of discoid lupus erythematosus obtained from exposed areas (where discoid lupus erythematosus usually occurs); it is absent, however, in sections taken from covered areas (Montgomery). In spite of its common occurrence in lupus erythematosus of exposed areas, basophilic degeneration of the collagen cannot be regarded in any way as diagnostic of lupus erythematosus because it occurs also in simple senile atrophy of the exposed skin (see page 157) as well as in many other dermatoses when located in exposed areas. The elastic tissue shows, irrespective of whether the section is obtained from an exposed or a nonexposed area, at first fraying and later destruction throughout the dermis wherever the inflammatory infiltrate occurs.

In the differential diagnosis, two diseases have to be considered which share with chronic discoid lupus erythematosus the presence of a patchy infiltrate—namely, secondary syphilis and lymphocytic lymphoma. Secondary syphilis differs from chronic discoid lupus erythematosus by the arrangement of the patchy infiltrate predominantly around blood vessels, by the presence of numerous plasma cells in the infiltrate and by the presence of vascular changes. In lymphocytic lymphoma, the patchy infiltrate is composed entirely of lymphocytes and does not show a tendency to arrangement near the epidermal appendages. Neither secondary syphilis nor lymphocytic lymphoma show epidermal changes comparable with those of chronic discoid lupus erythematosus.

Histopathology of Subacute Disseminate Lupus Erythematosus. The histologic changes in the lesions differ only in degree from those of chronic discoid lupus erythematosus. The atrophy of the epidermis, the liquefaction degeneration of the basal cells and the edema of the dermis are more prominent than in chronic discoid lupus erythematosus, whereas the hyperkeratosis and the inflammatory infiltrate are less marked.

Occasionally, the edema in the upper dermis and the liquefaction degeneration of the basal cells is severe enough to result in the formation of clefts and even vesicles between the epidermis and the dermis (McCreight and Montgomery). There may be evidence of fibrinoid

degeneration of the collagen (see under "Acute Systemic Lupus Erythematosus").

Histopathology of Acute Systemic Lupus Erythematosus. The fundamental lesion in acute systemic lupus erythematosus is fibrinoid degeneration of the collagen. Although this fibrinoid degeneration is best seen in the collagen of internal organs, usually it can be observed also in the skin. In order to study fibrinoid degeneration of the col-

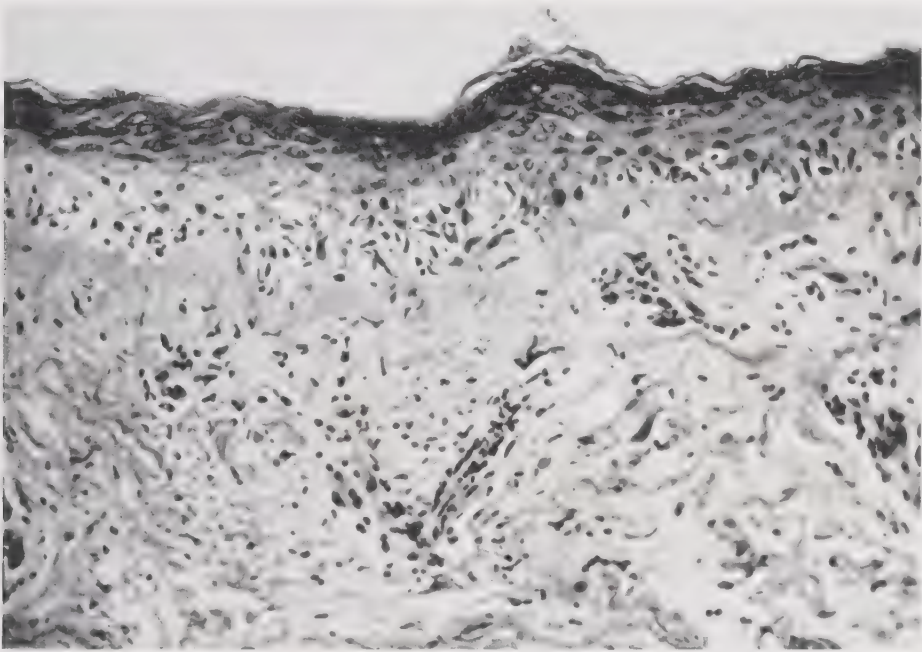


FIG. 143. Acute systemic lupus erythematosus. The epidermis is atrophic and shows marked liquefaction degeneration of the basal layer. The dermis shows fibrinoid degeneration. Only a mild perivascular inflammatory infiltrate is present. ($\times 200$)

lagen in the skin, sections should be taken from covered areas of the body; in exposed areas, basophilic degeneration of the collagen may blot out the finer changes of fibrinoid degeneration.

Fibrinoid degeneration of the collagen is characterized by changes both in the interfibrillary mucoid ground substance and in the collagen fibers themselves. The interfibrillary ground substance, normally not visible, becomes visible as homogeneous, intensely eosinophilic, refractile, "fibrinoid" clumps, while the collagen fibers become thickened, rigidly straight and more deeply eosinophilic than normally. In more advanced lesions, the degenerated collagen fibers become fragmented and fuse with the altered ground substance. The fibrinoid material shows metachromasia upon staining with toluidine blue and stains positive with the periodic acid-Schiff reaction.

Altshuler and Angevine believe that the fibrinoid material is formed by the precipitation of the acid mucopolysaccharides of the ground substance by an alkaline protein derived from either the necrosis of tissue or the interaction of the tissue with a damaging agent. The fibrinoid degeneration may affect the collagenous ground substance of capillaries, arterioles and venules. Thus, vascular damage, if pres-

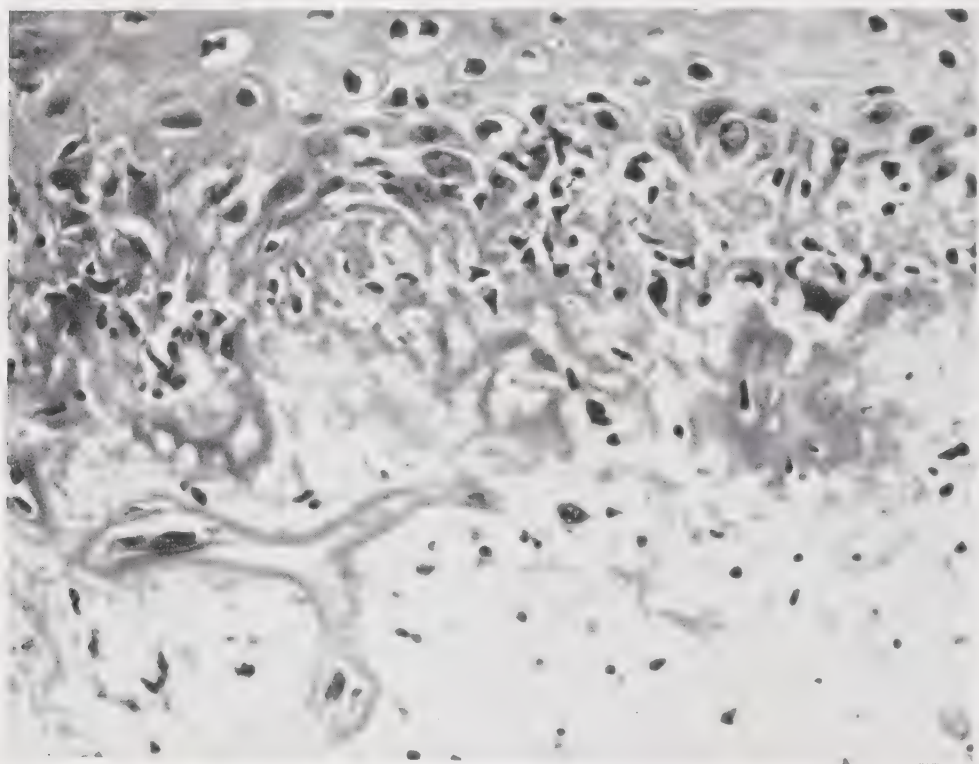


FIG. 144. Acute systemic lupus erythematosus. There are marked liquefaction degeneration of the basal layer and edema of the upper dermis. Within the zone of subepidermal edema, the collagen is present as homogeneous, "fibrinoid" material which lies in irregular conglomerates and, also, surrounds a capillary. ($\times 400$)

ent, does not represent an independent lesion but is part of the basic injury to the collagen (Klemperer, Pollack and Baehr, 1941).

The histologic appearance of the skin in acute systemic lupus erythematosus resembles that of subacute disseminate lupus erythematosus (Madden; Montgomery). One observes considerable liquefaction degeneration in the basal-cell layer and pronounced edema in the uppermost dermis (Fig. 143). Within the zone of subepidermal edema, homogeneous, eosinophilic, "fibrinoid" material may be seen lying in irregular conglomerates as well as around capillaries (Fig. 144). Deeper in the dermis, some of the collagen bundles are swollen and stain intensely eosinophilic. The inter-

fibrillary ground substance, normally not visible, may be present as homogeneous, eosinophilic, "fibrinoid" clumps (Fig. 143) (Klemperer, Pollack and Bachr, 1941). There is a rather mild perivascular infiltrate. In addition, one sees diffusely scattered histiocytes and fibroblasts, some of which show pyknosis of their nuclei. Extravasations of red blood cells are frequently observed. Changes in the walls of the vessels, other than edema, are usually absent. Only oc-

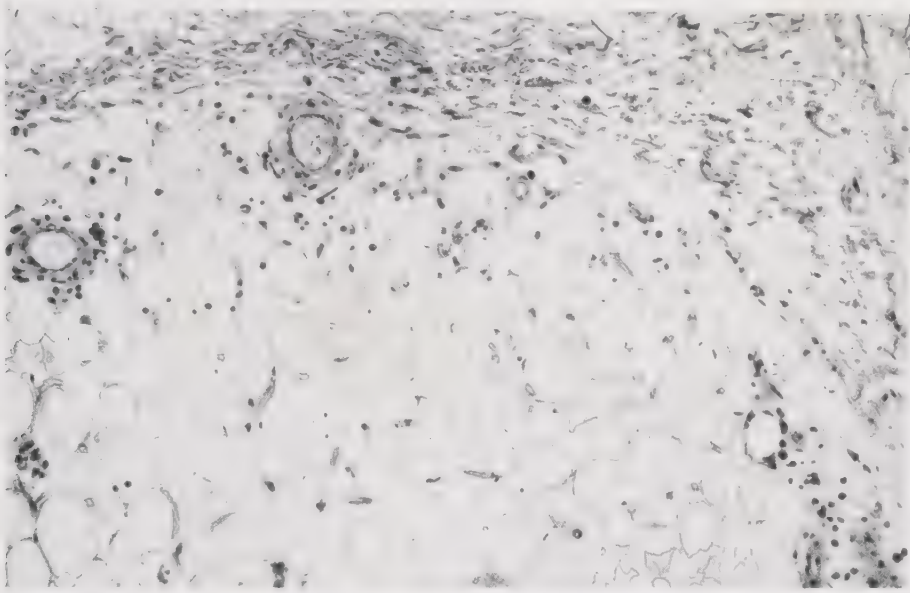


FIG. 145. Acute systemic lupus erythematosus, subcutaneous layer. The fat cells show mucoid degeneration. A scattered lymphocytic infiltrate is present. The collagen is increased in amount and shows fibrinoid degeneration. ($\times 100$)

casionally does one see degenerative changes in the walls. They are best demonstrated by the use of the periodic acid-Schiff reaction (Stoughton and Wells).

The subcutaneous fat is often involved. It may show focal mucoid degeneration with reactive lymphocytic infiltration. The collagen bundles separating the fat lobules may be increased in thickness and show edema and fibrinoid degeneration similar to those in the dermis (Fig. 145).

Histopathology of the Visceral Lesions of Acute Systemic Lupus Erythematosus. Visceral lesions usually are widespread but often minute in size, so that they may easily be overlooked on gross inspection and even on histologic examination unless they are especially looked for. The endocardium, the serous membranes, the heart and the skeletal muscle, the renal glomeruli, the spleen, the lymph nodes and the fat depots are affected most commonly.

The verrucous endocarditis of lupus erythematosus (the so-called Libman-Sacks syndrome) is caused by focal fibrinoid degeneration of the subendothelial connective tissue of the endocardium and the subsequent round-cell and fibroblastic proliferation and fibrosis. Since fibrinoid degeneration occurs again and again in the newly formed fibrous tissue, considerable amounts of granulomatous tissue are formed, resulting in raised verrucous formations (Libman and Sacks; Belote and Ratner; Gross; Klemperer, Pollack and Baehr, 1941).

The serous membranes, such as the pleura, the epicardium and the peritoneal covering of the liver and the spleen, may show fibrinoid degeneration of their collagen with mild, reactive inflammation composed of lymphocytes, plasma cells, histiocytes and fibroblasts (Klemperer, Pollack and Baehr, 1941).

The myocardium, and less frequently the skeletal muscle, may show small foci of degeneration in the interfascicular connective tissue and in the muscle bundles, usually associated with a mild reactive inflammation. These changes are identical with those of dermatomyositis, though much milder (Klemperer, Pollack and Baehr, 1941; Jager).

The renal glomeruli not infrequently present "wire-loop" lesions. In this type of lesion, individual glomerular loops appear thickened, rigid and deeply eosinophilic because of fibrinoid degeneration and thickening of the basement membrane of glomerular capillaries (Klemperer, Pollack and Baehr, 1941; Jager). In addition, small foci of necrosis may occur in some of the glomeruli (Jager).

Periarterial fibrosis of the central arteries in the spleen is one of the most common lesions in acute systemic lupus erythematosus. Thick, concentrically layered rings of sclerotic collagen fibers surround these arteries (Klemperer, Pollack and Baehr, 1941; Kaiser).

The lymph nodes often show foci of necrosis.

The body fat may show the same changes as those described for the subcutaneous fat.

Vascular changes are usually not conspicuous. Occasionally, however, the fibrinoid degeneration affects the collagenous ground substance of blood vessels. In rare instances, vascular changes are marked and resemble those of periarteritis nodosa (Jarcho; Mallory). It is possible that in these cases lupus erythematosus and periarteritis nodosa are present simultaneously.

Two structures are encountered frequently in acute systemic lupus erythematosus: L. E. cells in the blood and hematoxylin-staining bodies in the tissue. They are absent in chronic discoid and chronic disseminated lupus erythematosus. Since L. E. cells can be demon-

strated only very rarely in the blood of patients with diseases other than acute systemic lupus erythematosus, a positive test for L. E. cells is almost pathognomonic for it (Dubois).

The formation of L. E. cells is due to the presence in the plasma of a factor which causes disintegration of the nuclei of neutrophils, as well as of other cells, with subsequent phagocytosis of this material by neutrophils (Haserick; Gold). The L. E. cell is a neutrophil con-

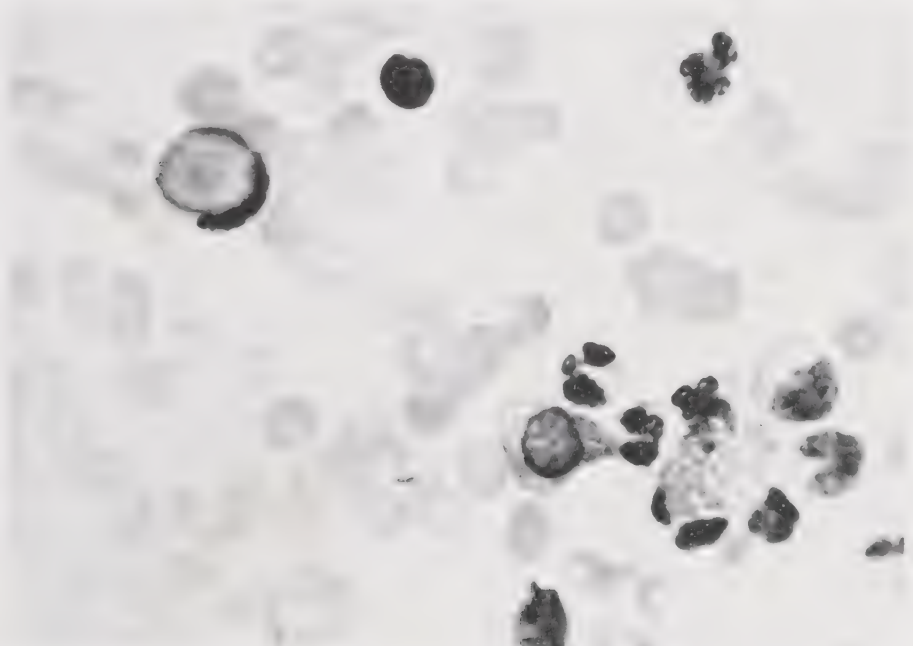


FIG. 146. **Acute systemic lupus erythematosus.** Smear of the buffy coat of a patient's blood after its incubation with heparin. In the left upper corner lies an L. E. cell: a neutrophil containing a large, smoky body. In the right lower corner, a rosette is seen consisting of amorphous material surrounded by phagocytizing neutrophils. ($\times 400$)

taining a round, structureless, smoky, basophilic mass of such size that it presses the lobes of the nucleus against the cell membrane (Fig. 146) (Hargraves, Richmond and Morton; Smith). L. E. cells can be demonstrated most easily in smears made from the buffy coat of the patient's blood after its incubation with heparin (Dubois). Smears of the buffy coat of heparinized sternal marrow may also be used. The smears are stained with Wright's stain. In addition to L. E. cells, one observes so-called rosettes. They consist of amorphous, nuclear material surrounded by neutrophils which are in the process of phagocytizing this material. The rosettes are precursors of the L. E. cell (Haserick).

The hematoxylin-staining bodies are found in various organs, especially in the kidney and the endocardium but also occasionally in the

skin (Klemperer, Gueft, Lee, Leuchtenberger and Pollister; Gueft). They appear in sections stained with hematoxylin and eosin as red-purple, homogeneous bodies of the size and the shape of fibroblasts or histiocytes. They may be present singly or in aggregates. They develop from degenerating nuclei and are identical with the smoky body within L. E. cells. Occasionally, one may see histiocytes or neutrophils which have phagocytized a hematoxylin-staining body. The similarity of these cells to L. E. cells is striking. Histochemical investigations have shown that, in the smoky bodies of L. E. cells and in the hematoxylin-staining bodies, the Feulgen reaction for desoxyribonucleic acid (DNA) is positive. This is evidence that they are derived from nuclear chromatin (Gueft).

Relationship of Acute Systemic Lupus Erythematosus to Dermatomyositis and Generalized Scleroderma. These three diseases—lupus erythematosus, dermatomyositis and scleroderma—are related to one another (Banks). The fundamental pathologic lesion, namely, fibrinoid degeneration of the collagen, is the same in all three diseases (Klemperer, Pollack and Baehr, 1941; Baehr and Pollack). Only the response to the fundamental lesion and the organs affected differ in these three diseases. One may summarize the response to fibrinoid degeneration of the collagen in these three diseases as follows:

In lupus erythematosus, the degeneration is associated with mild inflammation, occurring, as a rule, in small foci. The lesions are widespread.

In dermatomyositis, the degeneration is associated with usually pronounced inflammation. Lesions are present mainly in the skin and the striated musculature, but other organs, particularly the heart, may be involved.

In scleroderma, the degeneration is associated with only slight inflammation but with marked fibrosis. As in dermatomyositis, the principal lesions are in the skin and the striated musculature. In many cases, other organs (such as the heart, the esophagus, the lungs and the kidneys) are involved also.

The cause of fibrinoid degeneration of the collagen in these three diseases is not known. It is assumed by some that the degeneration represents an allergic, or hyperergic, reaction to infection, particularly streptococcal infection. However, Klemperer, Pollack and Baehr (1942) point out that, although fibrinoid degeneration of the collagen may occur in hypersensitivity reactions, it does not necessarily follow that all instances of fibrinoid degeneration are on the basis of hypersensitivity.

LUPUS ERYTHEMATOSUS PROFUNDUS (KAPOSI-IRGANG)

In this rare condition, cutaneous lesions of chronic discoid lupus erythematosus are present and, in addition, one or more firm, sharply outlined, movable subcutaneous nodes covered by normal-appearing skin.

Histopathology. The subcutaneous nodes show an infiltrate composed of lymphocytes as well as of histiocytes, plasma cells and sometimes neutrophils. Whereas Irgang and Arnold regard the nodes as a manifestation of lupus erythematosus, Pautrier feels that, because of the presence of foci of histiocytes, they represent subcutaneous sarcoid of Darier-Roussy. He concludes that lupus erythematosus profundus constitutes a coexistence of two different diseases—discoid lupus erythematosus and subcutaneous sarcoid of Darier-Roussy.

DERMATOMYOSITIS

In dermatomyositis, the skin and the skeletal muscles are predominantly affected.

The cutaneous lesions consist of extensive, rather sharply defined areas of erythema and edema involving predominantly the face, the chest and the arms. The eruption often greatly resembles that of subacute or acute lupus erythematosus. The lesions in the muscles cause progressive weakness, with vague muscular pain and later atrophy of the muscles. Involvement of the esophagus often results in dysphagia. Prior to the use of corticotropin or cortisone, the disease was often fatal. Even with its use, atrophy and fibrosis of the skin and the muscles may result, producing a clinical picture resembling that of generalized scleroderma.

Histopathology. In the skin, particularly in early lesions, the histologic changes may resemble those of subacute disseminate lupus erythematosus (Kinney and Maher; O'Leary and Waisman). Not infrequently, however, the histologic picture is that of a nonspecific chronic dermatitis. In old lesions, the collagen bundles of the dermis may show thickening, homogenization and sclerosis, and the cutaneous vessels fibrotic thickening of their walls so that the changes are indistinguishable from those of scleroderma (Dowling; Freudenthal).

The subcutaneous fat may show mucoid degeneration of the fat cells and focal lymphocytic infiltration in the early stage, and areas of fibrosis and calcification in the late stage (Norregaard; Wainger and Lever) (see "Calcinosis Cutis," page 276).

During the active phase of the disease, the skeletal muscles show

degenerative changes and inflammation. The degree of these changes varies not only in different muscles but also within each affected muscle. Even in severely affected muscles, close to areas of severe damage, one often finds areas of mild degeneration and areas in which the muscle bundles appear normal (Fig. 147). In areas of mild degeneration, the muscle bundles exhibit effacement of transverse striation,



FIG. 147. **Dermatomyositis; muscle.** The muscle bundles show various degrees of degeneration. In addition, one sees edema and focal collections of inflammatory cells. ($\times 100$)

coagulation or hyalinization of the sarcoplasm and proliferation of nuclei. In more severely degenerated areas, the muscle bundles show fragmentation of fibers, granular and vacuolar degeneration, basophilic staining and phagocytosis by large histiocytes. Inflammatory changes are secondary and not essential; they represent a reaction to the parenchymatous damage. One observes a cellular infiltrate, composed largely of lymphocytes, but containing also plasma cells, histiocytes and fibroblasts, between the muscle bundles, either in perivascular arrangement or distributed diffusely. In addition, edema usually separates the muscle bundles. The blood vessels are dilated, but, as a rule, their walls reveal no abnormalities (O'Leary and Waisman).

In older lesions, the changes in the muscles may resemble those of scleroderma. The muscle bundles show sclerosis and atrophy, and fibrotic connective tissue replaces the muscle bundles in many areas. On the basis of a study of these late changes, as just described in the skin and the skeletal muscle, several authors have concluded that dermatomyositis and generalized scleroderma represent one and the same disease (Dowling; Freudenthal).

Changes in organs other than the skin and the skeletal muscles occur, but not so regularly as in acute systemic lupus erythematosus or in generalized scleroderma. The heart may show changes identical with those in the skeletal muscle though less severe (Kinney and Maher; O'Leary and Waisman; Wainger and Lever). The body fat may be affected similarly as the subcutaneous fat (Greenway and Lambie; Kinney and Maher; Wainger and Lever). Inflammatory changes in the serous membranes may occur (Kinney and Maher). Ulcerative lesions in the gastro-intestinal tract due to vascular occlusions have been described (Karelitz and Welt; Horn; Wainger and Lever).

Of interest is the relatively common occurrence of visceral carcinoma in patients with dermatomyositis (Dostrovsky and Sagher). So far, 31 cases of carcinoma in dermatomyositis have been reported (Schuermann). In a statistical analysis, Schuermann concludes that carcinoma occurs at least five times more frequently in patients with dermatomyositis than in the normal population. In contrast with this, only one case of carcinoma in scleroderma has ever been reported.

POIKILODERMA ATROPHICANS VASCULARE (JACOBI)

Poikiloderma atrophicans vasculare has been described in a few instances as an independent disease (Marchionini and Besser; Dowling and Freudenthal; Downing, Edelstein and Fitzpatrick). As a rule, however, it occurs secondarily to other diseases of the skin. It occurs most frequently in dermatomyositis but also in lupus erythematosus and in mycosis fungoides (see page 484). When associated with dermatomyositis, the term poikilodermatomyositis is often employed.

Clinically, poikiloderma atrophicans vasculare presents large, ill-defined areas, usually in symmetrical distribution, which in the early stage show erythema and slight scaling, a mottled pigmentation and numerous telangiectases. In the late stage, the skin appears atrophic; the erythema has largely disappeared but the mottled pigmentation and the telangiectasia are more pronounced. The clinical picture then resembles chronic radiodermatitis.

Histopathology. In the idiopathic form of poikiloderma and in poikiloderma associated with dermatomyositis or lupus erythematosus, the histologic changes are identical. In the early active stage, the epidermis shows moderate atrophy of the stratum malpighii, effacement of the rete ridges and hydropic degeneration of the basal cells (Fig. 148). In the upper dermis, one finds a fairly dense cellular

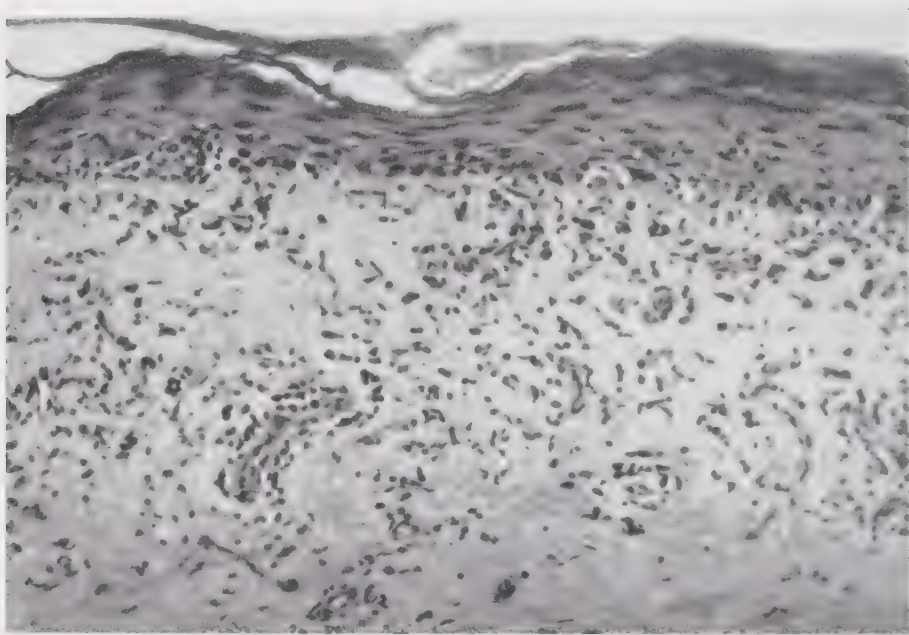


FIG. 148. **Poikilodermatomyositis, early stage.** The epidermis shows atrophy and hydropic degeneration of the basal cells. In the upper dermis, one sees a fairly dense inflammatory infiltrate, which in places invades the epidermis. The collagen of the upper dermis shows edema and hyalinization. ($\times 200$)

infiltrate, which in places invades the epidermis and often has a band-like arrangement. The infiltrate consists of lymphocytes, histiocytes and fibroblasts. Many melanophores may be present. Some of the superficial capillaries are dilated. The collagen is edematous and shows hyaline degeneration. The elastic tissue is largely destroyed. Hair follicles and sebaceous glands are absent (Horn).

In the late stage, the epidermis is atrophic. There is marked dilatation of superficial capillaries. The dermis shows homogenization and sclerosis of the collagen with little or no inflammatory infiltrate. Melanophores are present in varying numbers. In contrast with scleroderma, the dermis is greatly thinned (Guy, Grauer and Jacob).

In poikiloderma associated with mycosis fungoides, the histologic changes in the dermis are those of mycosis fungoides (see page 189).

Differential Diagnosis. Subacute disseminate lupus erythematosus, like poikiloderma atrophicans vasculare, shows atrophy of the stratum malpighii and vacuolization of the basal layer. However, the presence of the superficially located, bandlike infiltrate in poikiloderma atrophicans vasculare usually makes a differentiation possible.

SCLERODERMA

Two forms of scleroderma occur: circumscribed scleroderma (morphea) and systemic or generalized scleroderma.

Clinical Appearance. In circumscribed scleroderma (morphea), one or several round, oval or irregularly shaped, smooth, indurated patches are present. They are at first dull red or violaceous in color, but soon assume an ivory color. As long as there is peripheral extension, the patches tend to have a purplish halo ("lilac ring"). The disease is benign. Internal lesions are absent.

In systemic or generalized scleroderma, large areas of the skin are affected. At first, the involved areas present diffuse induration. As the disorder progresses, the skin and the subcutaneous tissue become firmly bound to the underlying structures, so that motion is difficult. Gradually, the skin and the subcutaneous tissue undergo atrophy, but, even at this stage, the skin retains some of its induration. The face and the hands are often the most severely affected areas ("acro-sclerosis"). In addition to the skin, the striated musculature invariably is affected, resulting in weakness and muscular atrophy. Involvement of the esophagus may lead to difficulties in deglutition; of the heart, to cardiac insufficiency; of the lungs, to dyspnea.

Histopathology of Circumscribed Scleroderma (Morphea). An early inflammatory and a late sclerotic stage exist. Most sections obtained routinely show a histologic picture intermediary between the two stages.

In the early lesion, the collagenous bundles appear swollen and homogeneous. They are separated by edema. An inflammatory infiltrate, predominantly lymphocytic, is present between the collagenous bundles and around blood vessels (Fig. 149). The walls of the vessels are edematous. These changes are present throughout the dermis. In addition, the inflammatory infiltrate extends between the fat cells of the subcutaneous layer, causing degeneration of the fat cells. The elastic fibers are frayed and may be destroyed.

In a late lesion, the dermis is markedly thickened. The collagen bundles are hypertrophic, sclerotic and closely packed (Fig. 150). Fibroblasts are fewer than in the normal dermis. The inflammatory infiltrate has disappeared almost completely, except around the vessels, where, as a rule, one still finds a few inflammatory cells. Most of

the vessels in the dermis show marked thickening and sclerosis of their walls with narrowing of their lumina. Sebaceous glands and hair structures are often completely absent. Sweat glands, on the other hand, are still present; they are reduced in number and are atrophic. Instead of lying close to the cutaneous-subcutaneous border and being surrounded by fat cells, they lie in the midst of sclerotic

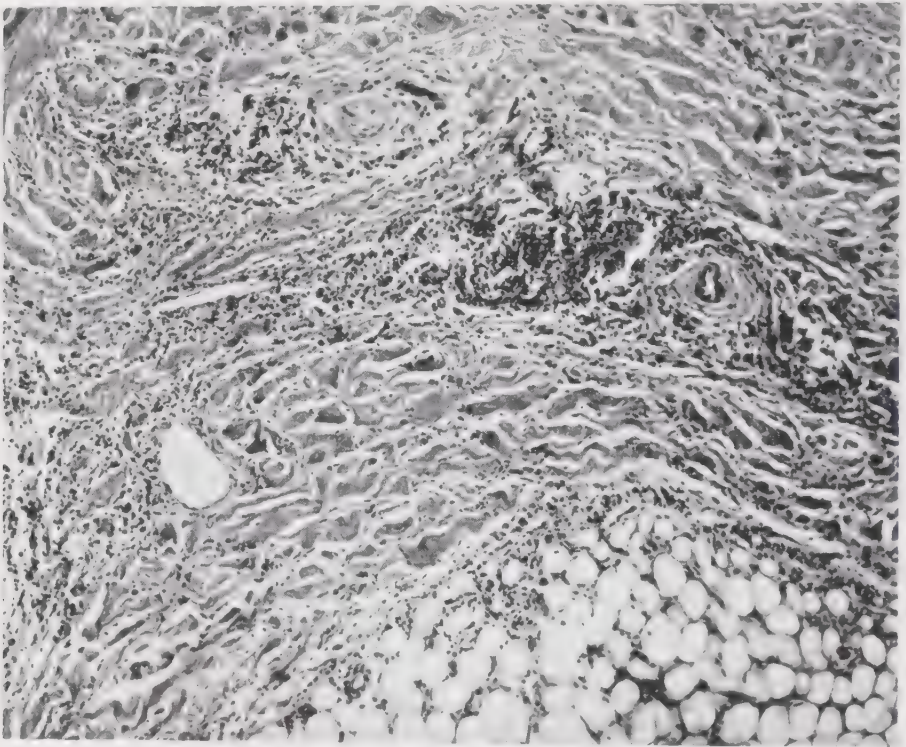


FIG. 149. Scleroderma, early stage. The collagenous bundles appear swollen and homogeneous and are separated by edema. An inflammatory infiltrate, predominantly lymphocytic, is present between the collagenous bundles. The wall of the blood vessel seen on the right side is thickened by edema and beginning fibrosis. ($\times 100$)

collagenous bundles, tightly "bound down" by them. The fact that the sweat glands lie inside the dermis rather than at its lower border is evidence that the thickening of the dermis is produced not alone by hypertrophy of the pre-existing collagen bundles but also by new formation of collagen at the lower border of the dermis. The border between the dermis and the subcutaneous layer is not so sharp as it usually is, because thick strands of sclerotic collagen extend from the dermis into the subcutaneous layer and replace much of the subcutaneous fat. The thickness of the subcutaneous layer may be greatly reduced. The vessels in the subcutaneous layer, including those of large caliber, often show marked thickening of all their coats with

narrowing of the lumen (O'Leary and Nomland). It is worth noting that the rete ridges of the epidermis usually remain well preserved in spite of the fact that the thickened collagen bundles extend right up to it.

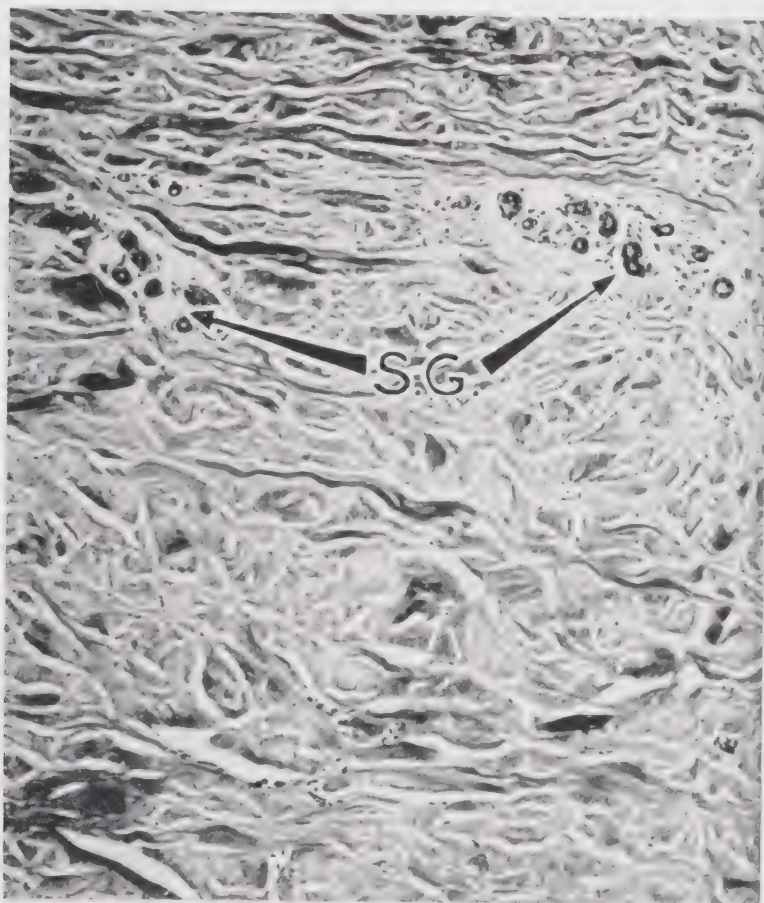


FIG. 150. Scleroderma, late stage. The collagen bundles are hypertrophic, sclerotic and closely packed together. Only very little inflammatory infiltrate is present. Fibroblasts are fewer than in the normal dermis. Groups of rather atrophic sweat glands (S.G.) are tightly bound down by collagen. ($\times 100$)

Histopathology of Generalized Scleroderma. The cutaneous changes are essentially the same as in circumscribed scleroderma, so that a histologic differentiation of the two types is not possible. In the early stage, degenerative changes are often more severe than in the circumscribed type. One may observe fibrinoid degeneration of the collagen (Pollack). The walls of the vessels may show marked intimal proliferation, fibrinoid degeneration and inflammatory infiltration (Masugi and Yä-Shu). An occasional vessel may show throm-

bosis. In the late stage, focal or even extensive calcification may take place in the lower dermis and in the subcutaneous layer (Talbot, Gall, Consolazio and Coombs; Brody and Bellin; Kanee). (See also "Calcinosis Cutis," page 276.) Also, in the late stage of generalized scleroderma, the epidermis may show, in contrast to circumscribed scleroderma, atrophy with disappearance of the rete ridges.

Histopathology of the Visceral Lesions of Generalized Scleroderma. There are often extensive systemic manifestations. The skeletal muscles are nearly always affected severely. In early lesions, degeneration of muscle bundles with accompanying inflammation, similar to dermatomyositis but less severe, may be observed occasionally. However, the characteristic changes are homogenization, sclerosis and atrophy of the muscle bundles with increase in the interstitial connective tissue. In contrast with dermatomyositis, the interseptal blood vessels often show marked obliterative changes. Foci of chronic inflammation may be present around the vessels. The musculature of the esophagus is often affected similarly (Lindsay, Templeton and Rothman). Extensive atrophy and fibrosis may occur in the heart muscle (Weiss, Stead, Warren and Bailey) and in the intestinal musculature (Bevans). Widespread sclerosis of the medium-sized and the small-sized vessels in the myocardium has been observed.

Pathologic changes may occur also in the endocardium and the epicardium (Pollack), in the serous membranes (Bevans) and in the esophageal and the intestinal mucosa (Bevans). The changes consist, in early lesions, of fibrinoid degeneration of the collagen with reactive inflammation, as in acute systemic lupus erythematosus. In older lesions, homogenization and sclerosis of the collagen predominate.

Additional findings in occasional instances include glomerulitis of the wire-loop type, as in acute systemic lupus erythematosus (Pollack; Bevans); extensive fibrosis with cystic changes in the lungs (Dostrovsky); and fibrosis of the thyroid (Bevans).

PERIARTERITIS NODOSA

Periarteritis nodosa is a manifestation of hypersensitivity. Although, in most cases, the cause of the disease is not apparent, the administration of foreign serum or of sulfonamides may be the cause (Rich). The disease affects mainly small arteries and arterioles, but occasionally also veins. The principal vessels affected are those of the gastro-intestinal tract, the kidneys and the heart; but those of the brain, the lungs and the skin as well as those of other organs may be involved.

Depending on the sites of involvement, the clinical symptoms may vary. Severe abdominal pain and symptoms of nephritis and of myocardial disease are the most common manifestations. Irregular fever and marked prostration are present. The disease is fatal in the vast majority of cases.

Cutaneous manifestations are found in about one third of the cases. They are manifold and may consist of macules, papules, nodules, petechiae, ecchymoses and necrotic ulcers (Fig. 151). Subcutaneous nodules, usually movable and painless, are observed occasionally (Ketron and Bernstein). In some cases, extensive areas of cutaneous hemorrhage with subsequent necrosis occur (Melcer and Venkei).

Histopathology. The name periarteritis is misleading, for the lesions actually represent a panarteritis. On a histologic basis, the changes which occur in the arteries and the arterioles may be divided into four stages (Arkin; Weir).

In the first, the degenerative stage, sections of the intima and the media undergo necrosis. The necrosis often affects only a segment rather than the entire circumference of the vessel, and only portions of the vessels are involved. Miliary aneurysms may form in areas of segmental necrosis.

In the second, the inflammatory stage, the necrotic area and the adjoining adventitia are densely infiltrated with polymorphonuclear leukocytes and eosinophils, and sometimes also with lymphocytes and plasma cells (Fig. 152). The infiltrate extends to the perivascular tissue. The lumen of most vessels thus affected is thrombosed.

In the third, the granulation stage, the necrotic part of the vascular wall is replaced by granulation tissue and the intima shows proliferation leading to partial or total occlusion of the lumen.

In the fourth, the fibrotic stage, the destroyed vascular wall is replaced by scar tissue. The lumen may show reduction in size, obliteration or recanalization.

In the skin, the arterioles at the cutaneous-subcutaneous border and in the subcutaneous tissue may show the typical changes of periarteritis nodosa (Fig. 151). However, the small blood vessels of the dermis show only occasionally necrotic changes in their walls. More commonly, these vessels show a vasculitis indistinguishable from that seen in anaphylactoid purpura (see page 127): an inflammatory infiltrate within and around the vessel walls composed largely of neutrophils and eosinophils, many of which show fragmentation of their nuclei. Thrombus formation, with or without inflammatory reaction, also may occur in the cutaneous vessels. The vasculitis and the throm-

bus formation cause extravasation of erythrocytes (Ketron and Bernstein).

It has been noted by several authors (Carol and Prakken; Miescher; Slinger and Starck) that periarteritis nodosa may occur in a benign,

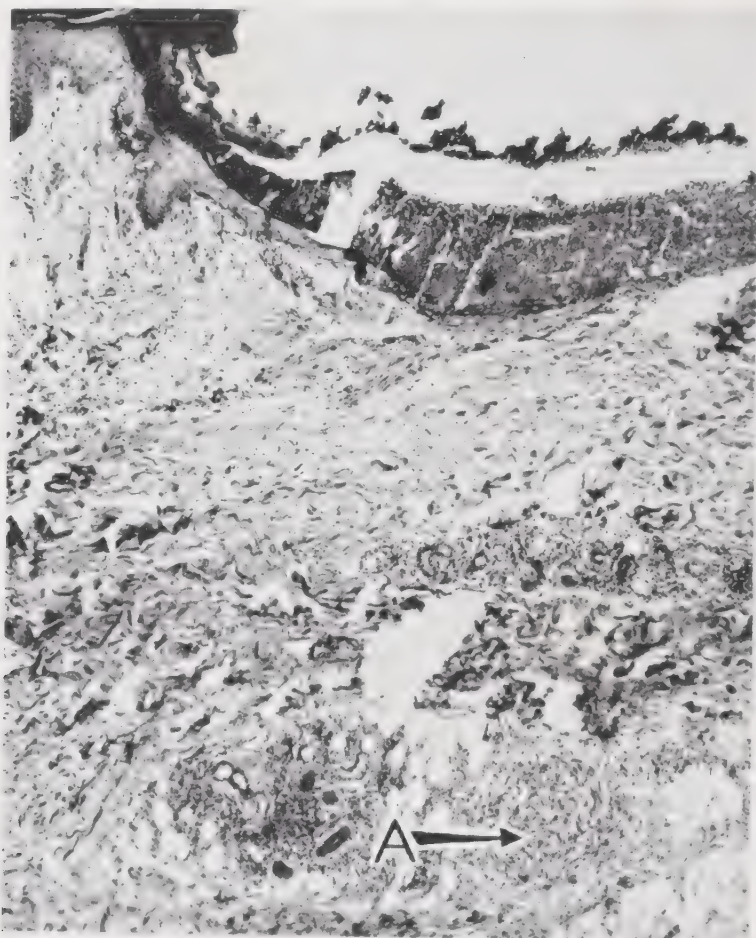


FIG. 151. *Periarteritis nodosa*. Low magnification. An artery (A) at the cutaneous-subcutaneous border shows the granulation stage of *periarteritis nodosa*. Above the artery is an ulcer which is probably caused by the occlusion of the artery. ($\times 50$)

chronic form limited to the skin and the subcutaneous tissue. These authors state that, histologically, the lesions of the benign form are indistinguishable from those of the malignant systemic form.

ALLERGIC GRANULOMATOSIS

An attempt has been made recently to divide *periarteritis nodosa* into two types: "true *periarteritis nodosa*" and "allergic granulomatosis" (Churg and Strauss; Strauss, Churg and Zak; Zeek). In the

latter group, allergic manifestations dominate the clinical picture to a much greater extent than in "true periarteritis nodosa." Most patients have severe asthma as the first symptom and, in addition to visceral manifestations, show extensive cutaneous lesions, including erythema multiforme-like lesions, purpura, intracutaneous and subcutaneous nodules. Blood eosinophilia is pronounced. The course is

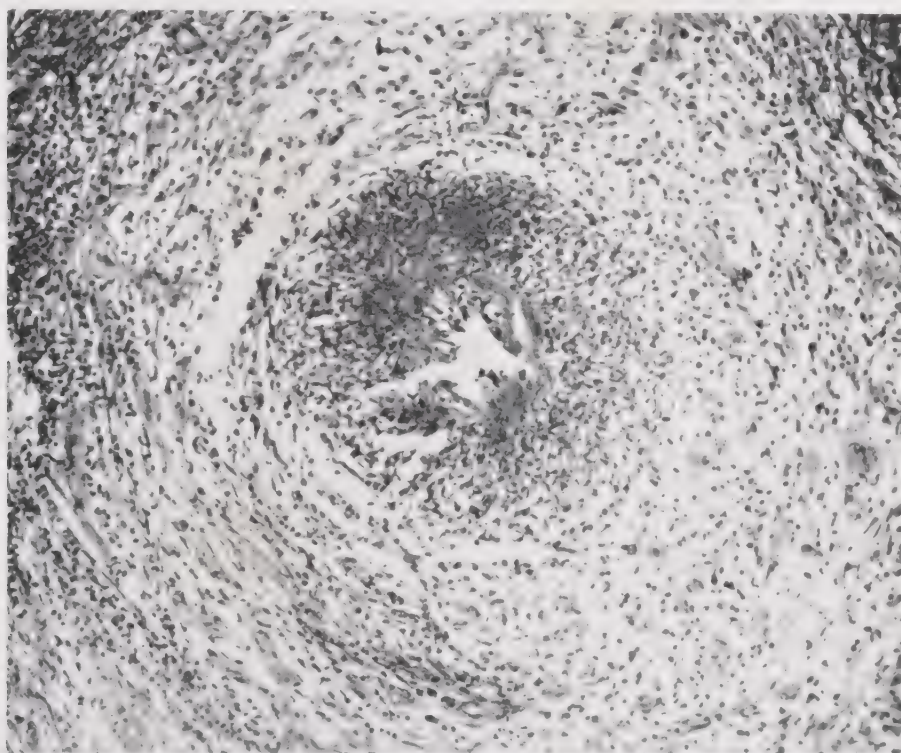


FIG. 152. *Periarteritis nodosa*. High magnification. A medium-sized artery located in the lower dermis shows partial necrosis of its wall and invasion by inflammatory cells. ($\times 200$)

chronic and usually fatal. Strauss, Churg and Zak believe that periarteritis nodosa as a result of drug sensitivity usually manifests itself as allergic granulomatosis.

Histopathology. Histologically, in addition to typical, widespread lesions of periarteritis nodosa, one finds extravascular granulomas in many organs. The cutaneous and the subcutaneous nodules show no necrotizing arteritis but only extravascular granulomas. They consist of areas of central necrosis surrounded by radially arranged histiocytes and foreign-body giant cells which are embedded in a diffuse inflammatory infiltrate rich in eosinophils (Strauss, Churg and Zak).

The purpuric lesions show the same appearance as those of anaphylactoid purpura (see page 127).

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18

Epidermal Tumors

HISTOGENESIS AND CLASSIFICATION OF EPIDERMAL TUMORS

The epidermal tumors may be divided into two classes, namely, tumors of the surface epidermis and tumors of the epidermal appendages. In each class, nevoid tumors (or hamartomas) and carcinomas occur.

Nevoid tumors, or hamartomas, are defined as benign neoplasms which usually arise, in accordance with the Cohnheim theory, from arrested embryonal cells, but occasionally may arise from immature, pluripotential cells that have formed during adult life. Carcinomas are malignant neoplasms which are composed, according to Hanse-mann's theory, of anaplastic cells. They usually arise from mature cells, due to their change into anaplastic cells; but embryonal cells may also occasionally change into anaplastic cells and thus give rise to carcinoma. Anaplastic cells are dedifferentiated cells which behave differently from embryonal cells (Foulds). They are autonomous, able to exist more independently than embryonal cells and, therefore, survive when carried away through the lymphatics and multiply as metastases.

Tumors of the Surface Epidermis. The tumors of the surface epidermis may be classified as follows:

1. Nevoid (benign) tumors
 - a. Nevus verrucosus (papilloma)
 - b. Epidermal cyst
2. Precancerous tumors
 - a. Keratosis senilis
 - b. Leukoplakia
3. Carcinomas
 - a. Squamous-cell carcinoma (epidermoid carcinoma)
 - b. Bowen's disease (intra-epidermal squamous-cell carcinoma)
 - c. Paget's disease

Tumors of the Epidermal Appendages. The nevoid tumors, or hamartomas, of this group can be divided, according to the decreasing degree of organization and differentiation observed in them, into

four groups: organic nevi, adenomas, benign epitheliomas and basal-cell epitheliomas. (See Table 6.) The carcinomas of the epidermal appendages can be divided into sebaceous-gland carcinomas, eccrine-gland carcinomas and apocrine-gland carcinomas.

The author has advanced the thesis that the organic nevi, the adenomas, the benign epitheliomas and the basal-cell epitheliomas develop from arrested, embryonal primary epithelial germ cells, and, as such, are "primary epithelial germ tumors." Since the primary epithelial germ is an embryonal structure (see Chart 1, page 4), the tumors developing from it can, accordingly, be regarded as nevoid tumors, or hamartomas. It is the author's belief that the organic nevi, the adenomas and the benign epitheliomas arise from primary epithelial germ cells which, prior to the onset of neoplasia, attained a certain degree of differentiation; whereas the basal-cell epitheliomas arise from primary epithelial germ cells which attained no, or only little, differentiation. In accordance with the potentiality inherent in the primary epithelial germ to differentiate into sebaceous glands, apocrine glands and hair, differentiation in the tumors developing from the primary epithelial germ can be toward either sebaceous-gland, apocrine-gland or hair structures (see Table 6). Pinkus recently has suggested that those tumors in this group which arise in later life—especially the basal-cell epitheliomas—do not necessarily arise from congenitally preformed epithelial germ rests but from immature, pluripotential cells forming in later life.

The organic nevi are composed of mature organic structures. The cutaneous adenomas show less differentiation than the organic nevi; nonetheless, well-developed glandlike structures are present. In the benign epitheliomas, there is a further step-down in respect to differentiation. The basal-cell epitheliomas are the least differentiated of the primary epithelial germ tumors.

Basal-cell epitheliomas are not considered carcinomas because they do not metastasize. Their origin from basal cells is doubted because their cells, in contrast with basal cells, do not possess intercellular bridges. They are believed to originate from the primary epithelial germ for the following reasons: (1) they occur only in areas where primary epithelial germ structures (sebaceous glands, apocrine glands or hair) are found; (2) the cells of undifferentiated basal-cell epitheliomas resemble the cells of primary epithelial germs as found in embryos from 4 to 6 months old (Fig. 1); (3) structures resembling sebaceous glands, tubular glands and hair are present in many basal-cell epitheliomas and (4) basal-cell epitheliomas frequently are seen in the same lesion with primary epithelial germ tumors of higher differentiation.

TABLE 6.—CLASSIFICATION OF THE NEVOID TUMORS OF THE EPIDERMAL APPENDAGES (PRIMARY EPITHELIAL GERM TUMORS)

	WITH SEBACEOUS DIFFERENTIATION	WITH APOCRINE DIFFERENTIATION	WITH HAIR DIFFERENTIATION
I. Organic hamartomas (organic nevi)	Sebaceous nevi: 1. Nevus sebaceus (Jadassohn) 2. Adenoma sebaceum (Pringle) 3. Senile sebaceous nevus 4. Fordyce disease	Apocrine nevi	Hair nevi
II. Organoid hamartomas (adenomas)	Sebaceous adenoma	Apocrine adenomas: 1. Syringocystadenoma papilliferum 2. Hidradenoma papilliferum	
III. Suborganoid hamartomas (benign epitheliomas)	Sebaceous epithelioma	Apocrine epitheliomas: 1. Syringoma 2. Cyldindroma 3. Myo-epithelioma	Hair epitheliomas: 1. Tricho-epithelioma (epithelioma adenoides cysticum) 2. Calcifying epithelioma
IV. Nonorganic hamartomas a. Differentiated basal-cell epitheliomas b. Undifferentiated basal-cell epitheliomas	Cystic basal-cell epithelioma	Adenoid basal-cell epithelioma	Keratotic basal-cell epithelioma

Some of the terms used to designate groups of tumors require definition.

NEVUS. This term is used in the literature in two different ways, referring either to a tumor composed of nevus cells (nevocellular nevus, pigmented nevus) or to a lesion originating from embryonal cells and composed of mature or nearly mature structures (organic nevi, such as nevus vasculosus, nevus sebaceus, nevus pilosus and nevus verrucosus). In order to avoid confusion, it is advisable to use the term nevus when referring to an organic nevus always with a qualifying adjective, so that nevus without qualifying adjective designates a tumor composed of nevus cells. According to Jadassohn, organic nevi are tumors and not hyperplasias because they develop on the basis of an abnormal germ anlage and not by an increase in the size and number of mature structures.

NEVOID TUMOR (HAMARTOMA). The term nevoid tumor is used widely as a designation for benign tumors of embryonal origin. However, this term lacks conciseness and therefore is unsatisfactory. The term hamartoma appears more satisfactory. This term, derived from the Greek word *hamartanein* (fail, miss, err) was coined by Albrecht as a designation for "tumorlike malformations showing a faulty mixture of the normal components of the organ in which they occur." Van der Valk enlarged the concept of hamartoma to include all benign tumors of embryonal origin with an organoid structure. Since no satisfactory term exists for the entire group of benign tumors of embryonal origin, the author has suggested that the meaning of the term hamartoma be extended to include all such tumors, even those with suborganoid and nonorganic structure. Thus, the tumors arising from the primary epithelial germ may be divided into organic hamartomas (organic nevi), organoid hamartomas (adenomas), suborganoid hamartomas (benign epitheliomas) and nonorganic hamartomas (basal-cell epitheliomas).

EPITHELIOMA. The term epithelioma is used by many authors as a synonym for carcinoma of the epidermis. Since, however, the true meaning of the word is tumor of the epithelium, the term may be used, as suggested by Jadassohn, as a designation of benign as well as malignant tumors of the epidermis, provided that a qualifying adjective is added. It would perhaps be best if, as Becker has suggested, the term epithelioma be reserved for benign epidermal tumors and carcinoma for malignant epidermal tumors.

1. TUMORS OF THE SURFACE EPIDERMIS

NEVUS VERRUCOSUS

Nevus verrucosus is known also under various other clinical designations, such as hard nevus, epidermal nevus, nevus unius lateralis, linear nevus, keratotic nevus and ichthyosis hystrix.



FIG. 153. **Nevus verrucosus.** There are marked hyperkeratosis, acanthosis and papillomatosis. The rete ridges are elongated. ($\times 50$)

The lesions may be single or multiple and usually are present at birth. They consist of verrucous growths of brownish color which often show linear configuration. Large horny excrescences may be present.

Histopathology. Nevus verrucosus shows hyperkeratosis, papillomatosis and acanthosis with elongation of the rete ridges (Fig. 153). Thus, it has the histologic appearance of a papilloma.

The degree of hyperkeratosis and papillomatosis differs considerably from lesion to lesion and depends on the size of the lesion. The thickness of the granular layer varies; areas of marked hyperplasia of the granular layer may alternate with areas in which it is atrophic.

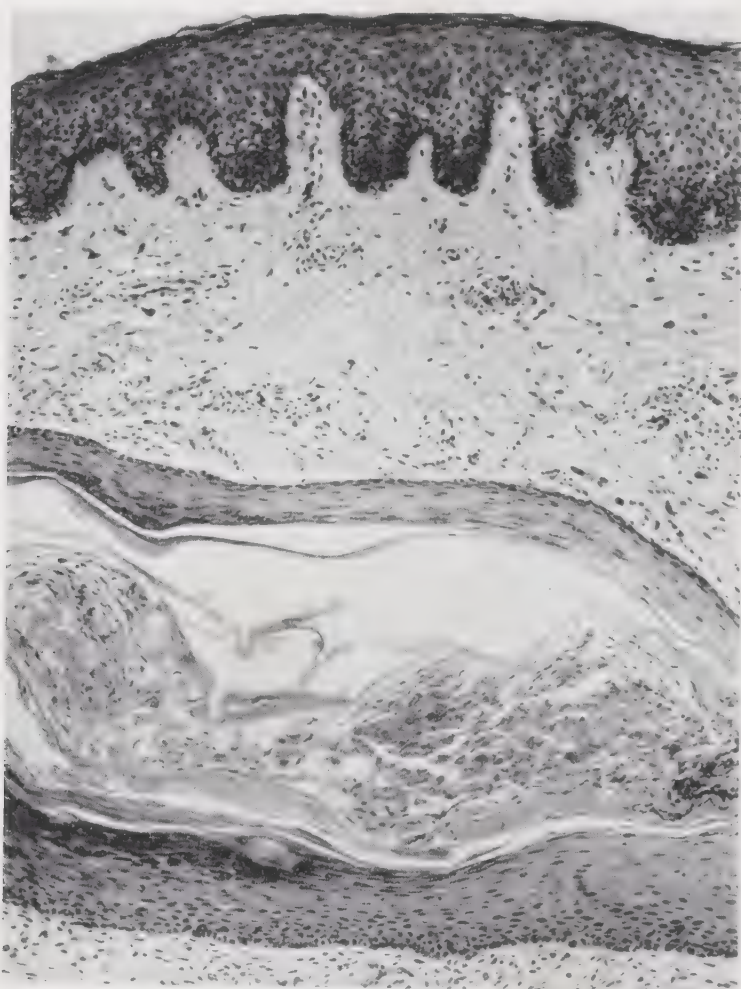


FIG. 154. **Epidermal cyst.** The wall is composed of true epidermis, i.e., squamous, granular and horn cells. The cyst is filled with keratin. ($\times 100$)

There may be some proliferation of basal cells (as seen in basal-cell papilloma) and hyperpigmentation of the basal layer. In rare instances, apocrine gland lumina are found deep in the dermis (see page 346). Nevus cells are absent in pure nevus verrucosus. However, the combination of nevus verrucosus and nevus pigmentosus is not infrequent, and in that case nevus cells are present.

Differential Diagnosis. Nevus verrucosus must be differentiated from other types of papillomas, namely: senile keratosis (*keratosis senilis*), basal-cell papilloma, verruca vulgaris and acanthosis nigri

cans. These five diseases all show hyperkeratosis and papillomatosis. In typical instances, differentiation is easy, but occasionally one is unable to make any more specific diagnosis in these diseases than papilloma. Because the term papilloma is often used in such non-

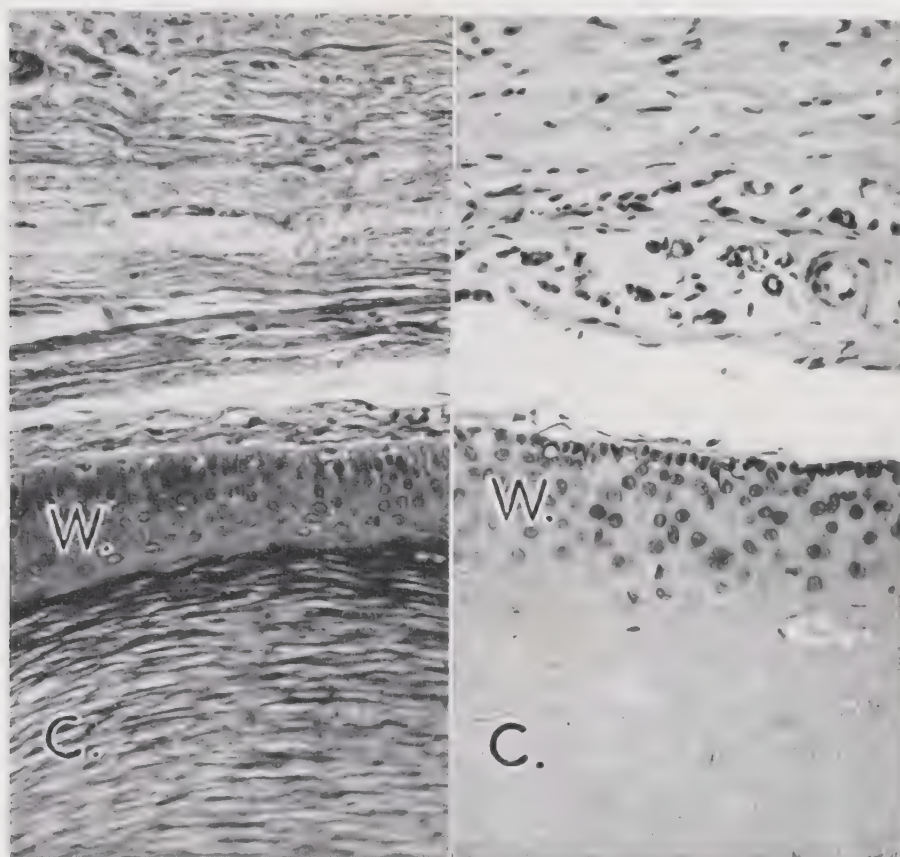


FIG. 155. Comparison of epidermal cyst (*left*) with sebaceous cyst (*right*). The wall (W.) of the epidermal cyst is composed of epidermis; the cyst (C.) contains layered keratin. The wall (W.) of the sebaceous cyst is composed of cells which possess no intercellular bridges and do not undergo keratinization. Many of the cells are vacuolated because of their transformation into sebaceous cells. The cyst (C.) is filled with amorphous material which has formed by the gradual disintegration of the vacuolated cells. ($\times 200$)

specific sense, it is better to avoid this term as a designation for nevus verrucosus.

In typical instances, keratosis senilis differs from nevus verrucosus by showing disorder of the epidermal cells and irregular downward proliferation of the epidermis (Fig. 157). Basal-cell papilloma shows marked proliferation of cells which resemble basal cells but show no intercellular prickles. In addition, deep invaginations of the horny layer are present resulting in the formation of horny pseudo-cysts (Fig.

203). *Verruca vulgaris* shows groups of large vacuolated cells in the upper stratum malpighii and the granular layer, and intermittent areas of parakeratosis (Figs. 118, 119). *Acanthosis nigricans*, as a rule, shows less acanthosis than *nevus verrucosus* and atrophy of the rete ridges rather than elongation (Fig. 139).

EPIDERMAL CYST (WEN), SEBACEOUS CYST, MILIUM, DERMOID CYST

Epidermal cysts and sebaceous cysts are often indistinguishable clinically. Both are commonly called wens. On histologic examination, most wens prove to be epidermal rather than sebaceous cysts. In their material, Warvi and Gates found 556 epidermal cysts as compared with only 3 sebaceous cysts.

Epidermal cysts are slow-growing, elevated, round, firm, intracutaneous or subcutaneous tumors, varying from 0.2 to 5 cm. in diameter. They occur most commonly on the scalp. As a rule, they are freely movable with the skin. No orifice can be demonstrated in the overlying skin. The material within them is nearly solid and is odorless.

Sebaceous cysts often cannot be differentiated from epidermal cysts on a clinical basis. In general, however, sebaceous cysts are softer than epidermal cysts, and, occasionally, they show a small orifice on their surface. The material within them is semifluctuant and has a rancid odor.

Milia are multiple pinhead-sized, whitish, globoid, hard lesions occurring most commonly on the face.

Dermoid cysts occur in rare instances in the subcutaneous tissue as soft, round or oval tumors of various sizes. The most frequently observed site is the periorbital region.

Histopathology. EPIDERMAL CYSTS have a wall composed of true epidermis, i.e., squamous, granular and horn cells (Fig. 154). Rete ridges may be present at the periphery of the wall. The cyst is filled with keratin, which frequently is arranged in laminated layers. Foci of calcification are found only in rare instances. When the cyst ruptures and the contents of the cyst reaches the dermis, a considerable foreign-body giant-cell reaction results. The foreign-body reaction may cause breaking up and partial disintegration of the epidermal cyst.

Malignant degeneration is rare, occurring in approximately 1.5 per cent of cases (Love and Montgomery). If such degeneration occurs, it takes the form of squamous-cell carcinoma. Usually, such carcinomas are of low-grade malignancy and do not cause metastases (Peden).

SEBACEOUS CYSTS, or steatomas, have a wall composed of epithelial cells that possess no intercellular bridges and do not undergo keratinization. Many of the cells are vacuolated because of their transformation into sebaceous cells (Fig. 155). The wall never possesses

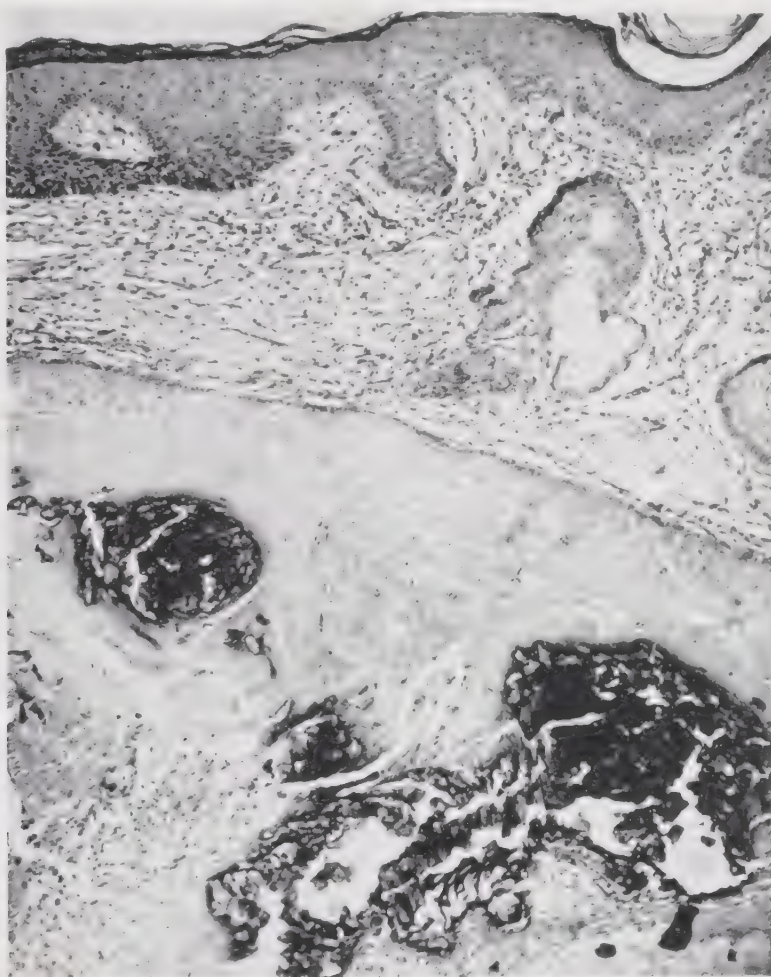


FIG. 156. Calcified sebaceous cyst. The palisading of the basal layer makes it evident that this is a sebaceous cyst. It has ruptured and fibrous tissue has proliferated into the lumen. ($\times 100$)

rete ridges at its periphery. The peripheral-cell layer shows a distinct palisade arrangement such as is never seen in epidermal cysts. The cysts are filled with amorphous material which forms by the gradual disintegration of the sebaceous cells. Large amounts of cholesterol and cholesterol crystals may be present in the cysts. Calcification occurs frequently within sebaceous cysts (Fig. 156). As in epidermal cysts, a considerable foreign-body reaction results when the wall of a sebaceous cyst ruptures, and the cyst may undergo partial disinte-

gration. In rare instances, basal-cell epitheliomas have been found arising in sebaceous cysts (Love and Montgomery).

MILIA present a histologic aspect similar to that of epidermal cysts. They are, however, much smaller. Milia are not tumors, like the epidermal and the sebaceous cysts, but are retention cysts caused by the occlusion of a pilosebaceous follicle (Love and Montgomery).

DERMOID CYSTS are lined by an epidermis endowed with rudimentary sebaceous glands, sweat glands and hair follicles. They contain sebaceous material as well as keratin. In addition, hairs are present in about 30 per cent of cutaneous dermoid cysts. Cartilage and bone are encountered occasionally (New and Erich).

Differential Diagnosis. For differentiation of epidermal and sebaceous cysts and, particularly, of sebaceous cyst with secondary basal-cell epithelioma from calcifying epithelioma, see page 368.

KERATOSIS SENILIS

Keratosis senilis occurs, frequently as multiple lesions, on the face and the dorsa of the hands in persons past middle life. The lesions

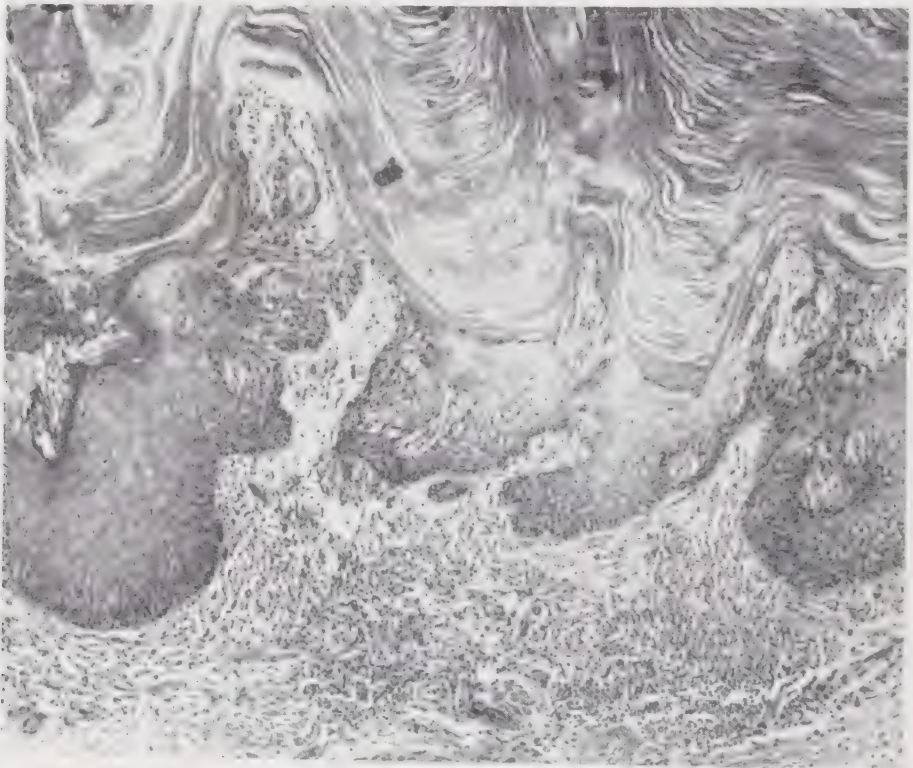


FIG. 157. Keratosis senilis. There are hyperkeratosis and papillomatosis. Areas of acanthosis alternate with those of atrophy of the stratum malpighii. The stratum malpighii shows irregular downward proliferation; the rete cells show disorderly arrangement. The upper dermis shows a rather pronounced chronic inflammatory infiltrate. ($\times 100$)

usually measure less than 1 cm. in diameter and show dry, hard scales firmly adherent to an erythematous base showing little or no infiltration. Occasionally, lesions of senile keratosis show a verrucous surface. In from 20 to 25 per cent of the cases of senile keratosis, squamous-cell carcinoma develops in one or more of the lesions (Montgomery and Dörffel).

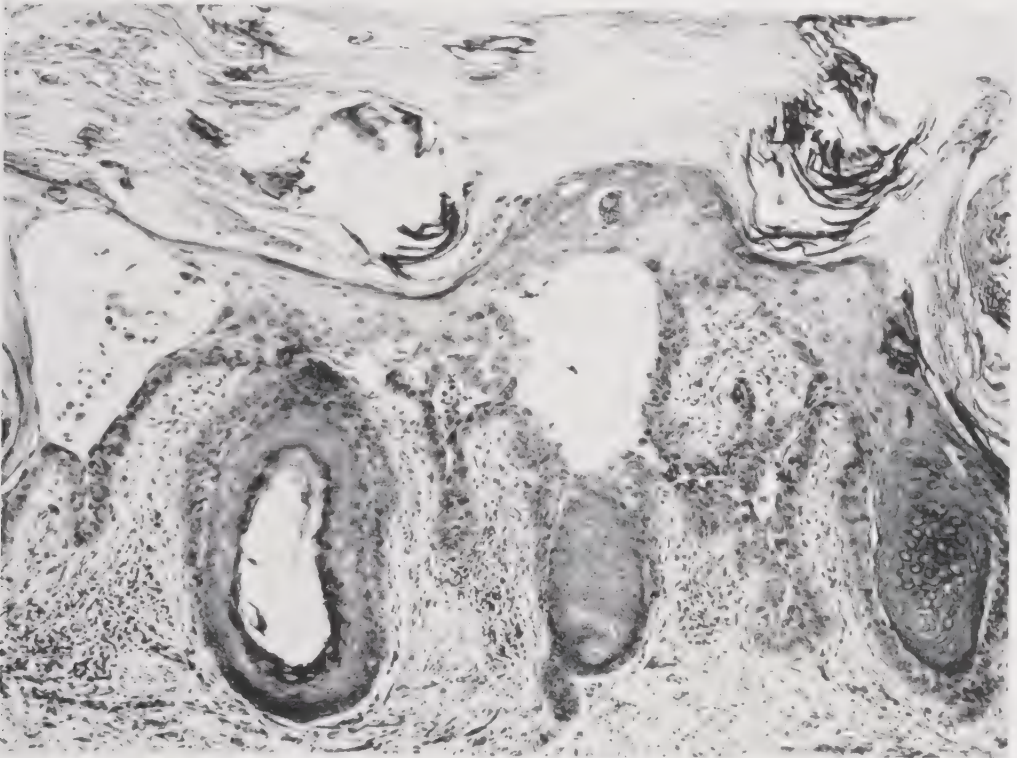


FIG. 158. Keratosis senilis. Clefts and two vesicles are present in the epidermis, predominantly in suprabasal location. A few acantholytic cells lie in the clefts. In addition, there is downward proliferation of basal cells into the dermis as short ductlike structures. There is atypicality of the epidermal cells. ($\times 150$)

Cornu cutaneum, a variant of keratosis senilis, shows a circumscribed horny excrescence sometimes suggesting the horn of an animal.

Histopathology. The shortest histologic definition that may be given to keratosis senilis is that it represents a "squamous-cell carcinoma, Grade $\frac{1}{2}$." It is a precancerous lesion, differing only in degree from squamous-cell carcinoma or Bowen's disease.

Hyperkeratosis is usually pronounced. Mild or moderate papillomatosis may be present. The stratum malpighii varies in thickness; areas of acanthosis and areas of atrophy may alternate. The stratum malpighii shows disorderly arrangement of the rete cells. In some cases, atypicalities such as vacuolization of cells, individual cell

dyskeratosis, clumping of nuclei and prevalence of mitotic figures are observed, so that the histologic picture approaches that of Bowen's disease (Szodoray). In other cases, the epidermis shows irregular downward proliferation but without frank invasion (Fig. 157). The histologic picture then approaches that of squamous-cell carcinoma, Grade I.

Not infrequently, immediately above the basal layer, one observes clefts similar to those seen in Darier's disease (see page 48). These clefts, first described by Freudenthal, may contain a few acantholytic cells. In rare instances, even small suprabasal vesicles may be present. The basal layer underneath these clefts and vesicles usually consists of cells with large, hyperchromatic nuclei which appear closely set together. In addition, this type of atypical basal layer may proliferate into the dermis as short ductlike structures and, furthermore, it may surround as cell mantles the upper portion of pilosebaceous follicles and sweat ducts the epithelium of which otherwise appears normal (Fig. 158) (Halter).

The upper dermis usually shows a fairly dense, chronic, inflammatory infiltrate in which plasma cells are prominent.

In instances in which a diagnosis of senile keratosis is made, it often is advisable to section deeper into the block of tissue, because actual progression into squamous-cell carcinoma may have taken place in another area.

CORNU CUTANEUM is a type of keratosis senilis with particularly pronounced hyperkeratosis.

Differential Diagnosis. Keratosis senilis must be differentiated from verruca senilis, or basal-cell papilloma, in which one finds proliferation of cells of the basal-cell type (see page 382) (Freudenthal; Montgomery and Dörffel; Ruiter). For differentiation from squamous-cell carcinoma, see page 334; from arsenical keratosis, see page 155.

LEUKOPLAKIA

Leukoplakia represents senile keratosis of the mucous membranes and occurs on the lips, the oral mucosa and the vulva. On the vulva, leukoplakia is apt to develop secondary to senile atrophy of the vulva (see page 162).

Clinically, the lesions consist of white patches which are sharply demarcated, irregular in outline and slightly elevated above the level of the mucous surface. The lesions are often multiple and may be discrete or confluent. In from 20 to 30 per cent of the cases of leukoplakia, squamous-cell carcinoma supervenes (MacKee and Cipollaro).

Histopathology. In leukoplakia, hyperkeratosis usually is less pronounced than in keratosis senilis, but the inflammatory infiltrate is

often more intense and may hug the epidermis just as in lichen planus. Formation of suprabasal clefts, as in senile keratosis, does not occur.

Differential Diagnosis. Differentiation of leukoplakia from lichen planus may be very difficult and occasionally impossible. As a rule, however, the infiltrate in leukoplakia is less severe than in lichen planus and contains a rather large number of plasma cells, whereas, in lichen planus, their number is small. In both diseases, the epidermal-dermal border is apt to have a hazy outline due to the invasion of the lower epidermis by the inflammatory infiltrate, but only leukoplakia shows atypicality of the cells in the stratum malpighii. On the buccal mucosa, pressure of teeth or dentures may produce "pressure calluses" which show hyperkeratosis, acanthosis and a non-specific inflammatory infiltrate. They differ from leukoplakia by the absence of atypicality in the epidermis.

SQUAMOUS-CELL CARCINOMA (EPIDERMOID CARCINOMA)

Squamous-cell carcinoma may occur anywhere on the skin, as well as on the mucous membranes. It may begin as such or develop from a senile keratosis or leukoplakia. Most commonly, the lesion consists of a shallow ulcer surrounded by a wide, elevated and indurated border. The ulcer often is covered by a crust which conceals a red, granular base. Occasionally, raised, fungoid, verrucous lesions without ulceration occur. The latter are usually of a relatively low grade of malignancy, whereas ulcerated lesions may grow rapidly and cause metastases within a short time.

Histopathology. Squamous-cell carcinoma is a true, invasive carcinoma of the surface epidermis. On histologic examination, one finds the tumor to consist of irregular masses of epidermal cells, which proliferate downward and invade the dermis. The invading tumor masses are composed in varying proportions of differentiated squamous and horn cells and of de-differentiated (anaplastic, atypical) squamous cells. The more malignant the tumor, the greater is the number of atypical squamous cells. Atypicality of squamous cells expresses itself in changes such as great variation in the size and the shape of the cells, hyperplasia and hyperchromasia of the nuclei, absence of prickles, keratinization of individual cells, prevalence of mitotic figures and presence of atypical mitotic figures.

Differentiation in squamous-cell carcinomas is in the direction of keratinization. Keratinization often takes place in the form of horn pearls. The horn pearls are very characteristic structures, composed of concentric layers of squamous cells showing gradually increasing

keratinization toward the center. The center may or may not show complete keratinization.

Broders introduced a system of grading squamous-cell carcinoma. He established four grades according to the proportion of differentiated cells to atypical cells. In Grade I, more than 75 per cent; in Grade II, more than 50 per cent; in Grade III, more than 25 per cent; and in Grade IV, less than 25 per cent of the cells are differentiated. Since differentiation is in the direction of keratinization, the degree of keratinization is a good guide in grading. Broders' system of grading is most useful and has been accepted widely in spite of certain objections raised against it. In the first place, there is, of course, a large personal factor in the interpretation of cytologic changes, and, secondly, different degrees of malignancy may be present in different fields. In regard to the first objection, Broders has suggested to err rather on the side of the higher grade because malignant processes tend to be progressive rather than regressive. In regard to the second objection, one should examine several sections of every tumor and grade according to the least differentiated portion (Edmundson).

In squamous-cell carcinoma, Grade I (Fig. 159), the tumor masses have not penetrated beyond the level of the sweat glands. They still show in some areas an intact basal layer at their periphery. In other areas, the basal layer has become disorganized and has disappeared. In such areas, the cell masses appear poorly demarcated from the surrounding stroma. The cells of the invading cell masses are predominantly mature squamous cells with well-developed prickles. Nevertheless, some of the squamous cells are atypical. Horn pearls are present in fairly large number. Some are well developed and have fully keratinized centers; others, however, show only partial keratinization of their centers and the concentric arrangement of the cells is not distinct. Besides horn pearls, sheets of partially keratinized cells may be present. The dermis often shows a rather marked inflammatory reaction. It is noteworthy that, in senile keratosis and squamous-cell carcinoma, Grade I, the inflammatory reaction in the dermis is usually much more pronounced than in the more malignant forms of squamous-cell carcinoma. This phenomenon is due to the fact that tissue, when invaded by carcinomatous cells, is able to defend itself to some extent, provided the cells are only moderately malignant, but is overwhelmed without any fight if the cells are highly malignant. (The same observation, incidentally, can be made also in malignant melanoma and mycosis fungoides—see pages 460 and 485.) Metastases do not, as a rule, occur as long as a squamous-cell carcinoma remains Grade I.

In squamous-cell carcinoma, Grade II (Fig. 160), the invading cell masses are, as a rule, poorly demarcated from the surrounding stroma. They may invade deeply. Keratinization is much less in evidence than in Grade I. There are only few horn pearls, and those present show incompletely keratinized centers. A fairly large number of the squamous cells are atypical.

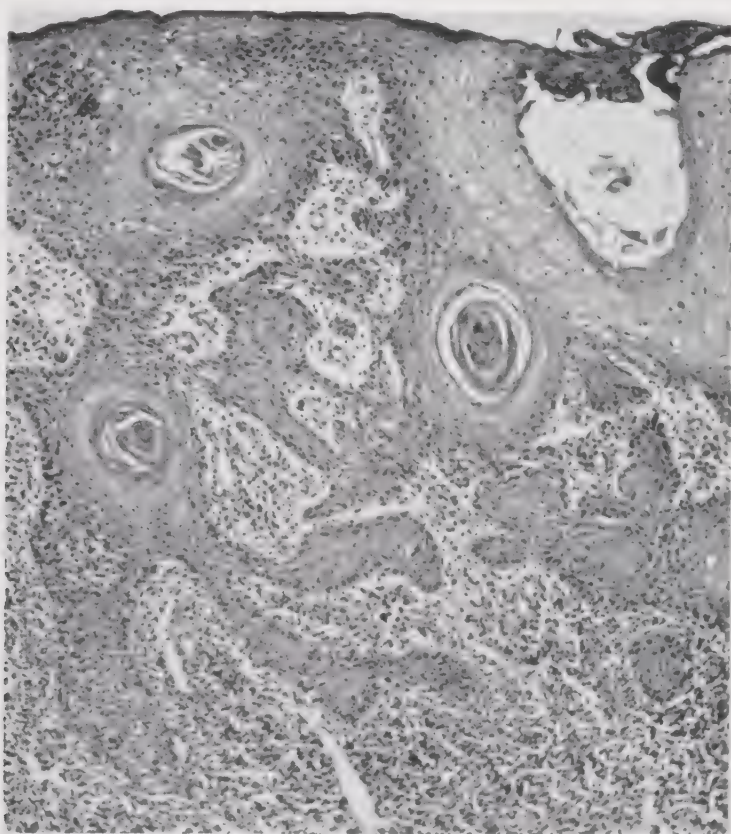


FIG. 159. Squamous-cell carcinoma, Grade I. There is invasion of the dermis by epidermal masses. The cells of the invading epidermal masses are predominantly mature squamous cells showing relatively slight atypicality. Several horn pearls are present. The dermis shows a marked inflammatory reaction. ($\times 100$)

In squamous-cell carcinoma, Grade III (Fig. 161), keratinization is minimal. Horn pearls are not found. Instead, keratinization occurs in small cell groups and in individual cells ("individual cell keratinization," "malignant dyskeratosis," see page 499). The majority of cells are atypical. Mitotic figures are conspicuous and often atypical.

In squamous-cell carcinoma, Grade IV (Fig. 162), keratinization is almost completely absent. Nearly all squamous cells are atypical and devoid of prickles. Thus, it is often difficult to arrive at the correct

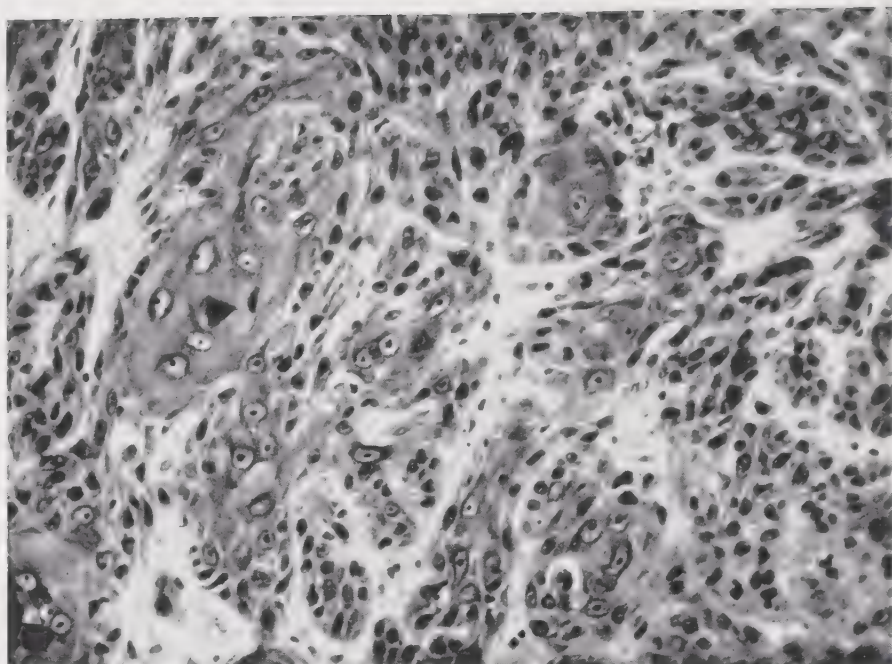


FIG. 160. Squamous-cell carcinoma, Grade II. The cell masses show much less keratinization than in Grade I. There are only few horn pearls and those present show incompletely keratinized centers. Atypical cells are conspicuous. ($\times 200$)



FIG. 161. Squamous-cell carcinoma, Grade III. No horn pearls are present. Keratinization occurs only in small cell groups. Many cells are atypical and devoid of prickles. To the right, a cell shows "individual cell keratinization" (I.K.). ($\times 200$)

diagnosis as long as individual fields only are studied. The tumor may suggest a malignant melanoma in some cases and a sarcoma in others. The latter diagnosis may be particularly difficult to rule out when the cells, as occasionally occurs, are spindle-shaped ("spindle-cell" squamous-cell carcinoma) (Brooks; Underwood, Montgomery and Broders). If, however, sections are subjected to a thorough study, the type of origin from the epidermis and the presence in a few areas

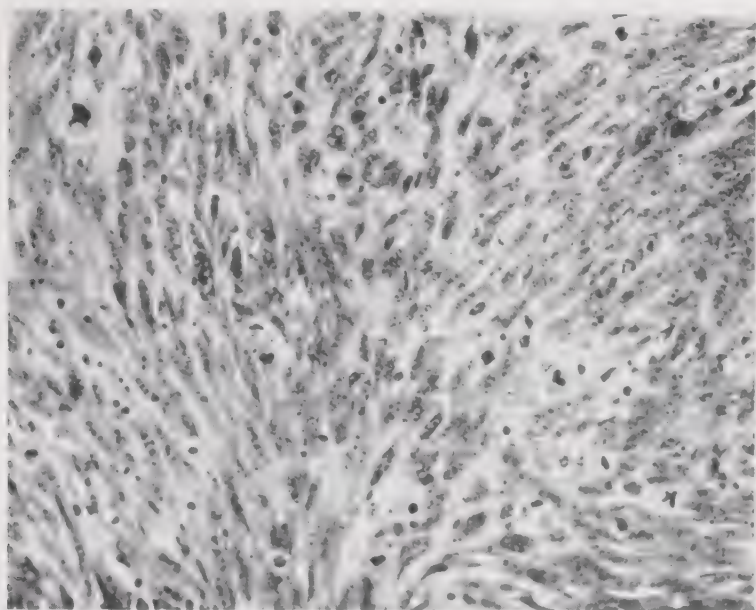


FIG. 162. Squamous-cell carcinoma, Grade IV. There is no evidence of keratinization. The epithelial cells appear atypical, are devoid of prickles and elongated, so that the tumor suggests a sarcoma almost more than a carcinoma. There are numerous mitotic figures. ($\times 200$)

of cells showing prickles or partial keratinization usually establish the diagnosis. Squamous-cell carcinoma, Grade IV, is relatively rare in the skin. Many of the reported instances of "spindle-cell" squamous-cell carcinoma occurred in areas of radiodermatitis. In this connection, it may be pointed out that it is not yet established fully whether or not sarcomas can develop following radiodermatitis. Most, if not all, cases reported as such in the literature represent squamous-cell carcinomas of the spindle-cell type (Sims and Kirsch; Gentele) (see page 122).

Metastases are rare in squamous-cell carcinoma, Grade I, but common in the other grades. The regional lymph nodes are the first site to be invaded by metastases.

Differential Diagnosis. The diagnosis of squamous-cell carcinoma, although easily made in typical cases, may be difficult at times.

Squamous-cell carcinoma must be differentiated from senile keratosis, pseudo-epitheliomatous hyperplasia and basal-cell epithelioma.

The differences between squamous-cell carcinoma and senile keratosis lie in the degree rather than in the type of changes. In both conditions, one finds atypicality of cells with dyskeratosis of individual cells and downward proliferation of the epidermis. However, in squamous-cell carcinoma these changes are more severe, and, in addition, horn pearl formation and actual invasion of the dermis are present. No sharp line of separation exists between the two conditions, and it is not infrequent to find in a lesion which in general has the appearance of senile keratosis, on serial sections, one or several areas in which the changes have progressed to squamous-cell carcinoma.

For differentiation from pseudo-epitheliomatous hyperplasia, see below. For differentiation from basal-cell epithelioma, see page 380.

PSEUDO-EPITHELIOMATOUS HYPERPLASIA

Considerable thickening and irregular proliferation of the skin, which clinically, as well as histologically, may suggest carcinoma, occurs not infrequently in chronic granulomas, such as bromoderma, blastomycosis and granuloma inguinale, and at the edges of chronic ulcers, such as occur after burns, in stasis dermatitis, basal-cell epithelioma, lupus vulgaris, scrofuloderma, gumma and pyoderma gangrenosum. In addition, granular-cell myoblastoma is known to evoke quite frequently a pseudo-epitheliomatous hyperplasia.

Histopathology. Histologically, one observes an epithelial hyperplasia which may closely resemble squamous-cell carcinoma. Grades I or II, and therefore is referred to as pseudo-epitheliomatous hyperplasia. Although squamous-cell carcinoma may develop at the edges of chronic ulcers, it is likely that some of the cases that have been regarded as such in the past were in reality pseudo-epitheliomatous hyperplasia.

The histologic picture of pseudo-epitheliomatous hyperplasia shows irregular invasion of the dermis by epidermal cell masses with horn pearl formation and often numerous mitotic figures (Fig. 163). The penetration may extend even below the level of the sweat glands as isolated fragments of epidermal tissue (Sommerville). However, the squamous cells usually are well differentiated, and atypicalities, such as individual cell keratinization and nuclear hyperplasia and hyperchromasia, are absent. Furthermore, in pseudo-epitheliomatous hyperplasia, there often are invasion of the epithelial proliferations by leukocytes and disintegration of some of the epidermal cells, a phe-

nomenon usually not seen in squamous-cell carcinoma (Winer; Montgomery). But even when all these criteria are taken into account, it may still be difficult to differentiate between squamous-cell carci-

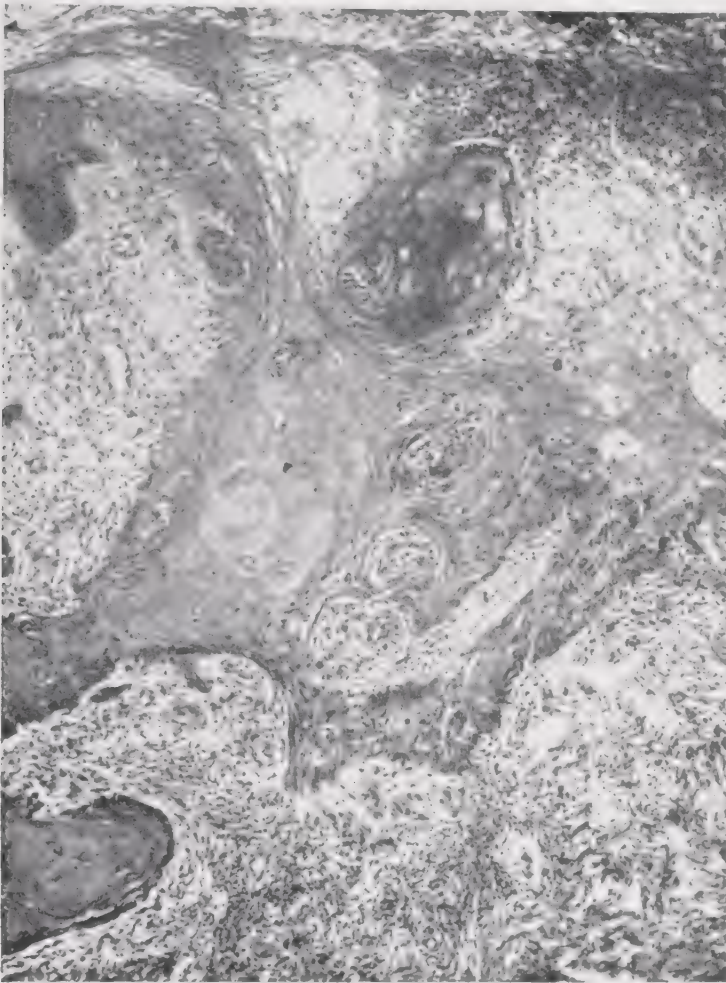


FIG. 163. Pseudo-epitheliomatous hyperplasia in bromoderma. There is downward proliferation of the epidermis analogous to squamous-cell carcinoma, Grade I. In the field shown, it is impossible to rule out carcinoma. Note, however, the permeation of the epidermis in many areas by inflammatory cells. ($\times 100$)

noma and pseudo-epitheliomatous hyperplasia by the study of histologic sections alone (Sommerville). Clinical data may be necessary for differentiation.

It is worth remembering to study the inflammatory infiltrate in every section in which one contemplates a diagnosis of squamous-cell carcinoma, Grades I or II, for evidence of either tuberculosis, syphilis or the granulomatous mycoses. If such evidence is found, one may

be dealing with pseudo-epitheliomatous hyperplasia rather than with squamous-cell carcinoma.

"MULTIPLE, PRIMARY, SELF-HEALING SQUAMOUS-CELL
CARCINOMATA"

In this disorder, which often is familial, there is a continuous appearance, especially on the face and the extremities, of papules which grow into nodules, ulcerate and, after a few months, heal with a depressed scar.

Histopathology. The histologic appearance is like that of a well-differentiated, keratinizing squamous-cell carcinoma, Grade I. A dense inflammatory infiltrate is present. There may or may not be ulceration, depending on the stage of the lesion.

It is generally agreed that differentiation from squamous-cell carcinoma is impossible on a histologic basis and depends on the clinical data (Smith; Sommerville and Milne; Witten and Zak).

The histogenesis is not clear. However, it is certain that the epidermal proliferation represents a pseudo-epitheliomatous hyperplasia. Whimster assumes that all the downward prolongations of epithelium can be explained as extreme hyperplasia, probably inflammatory in origin, of sweat ducts and hair follicles.

BOWEN'S DISEASE

Bowen's disease usually manifests itself as a single lesion. It is characterized by a dull-red patch of sharp but irregular outline, showing little or no infiltration. Within the patch, there usually are areas of crusting, beneath which one finds a granular and oozing surface. The patch slowly spreads by peripheral extension and shows no tendency to healing in its center.

Histopathology. Bowen's disease is an intra-epidermal, squamous-cell carcinoma, or a squamous-cell carcinoma in situ, and not a "pre-cancerous dermatosis," under which title it was described originally by Bowen.

The epidermis shows hyperkeratosis with parakeratosis, and acanthosis. The rete ridges are elongated and thickened, often to such a degree that the papillae located between them are reduced to thin strands or are obliterated. However, the basal layer is intact, and no true invasion can be seen. Throughout the stratum malpighii, the cells lie in complete disorder; many are atypical, showing large and hyperchromatic nuclei. Multinucleated epidermal cells containing clusters of nuclei are common (Fig. 164). Some cells may show marked vacuolization simulating Paget cells. However, the intercellular

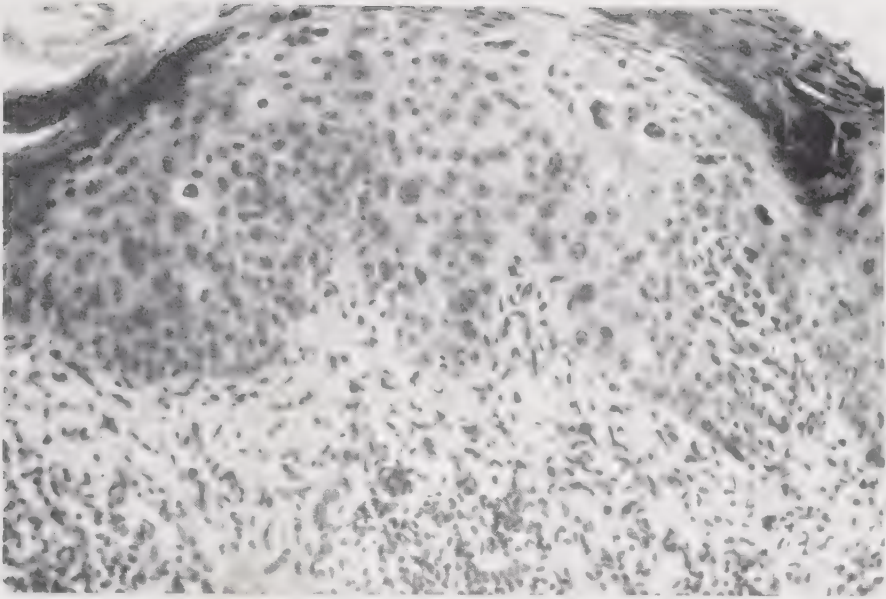


FIG. 164. **Bowen's disease.** The epidermis is thickened, the basal layer is intact. The cells of the stratum malpighii lie in complete disorder and many of them are atypical, showing large and hyperchromatic nuclei. Several multinucleated cells with clumped nuclei and numerous mitotic figures are present in the stratum malpighii. ($\times 200$)

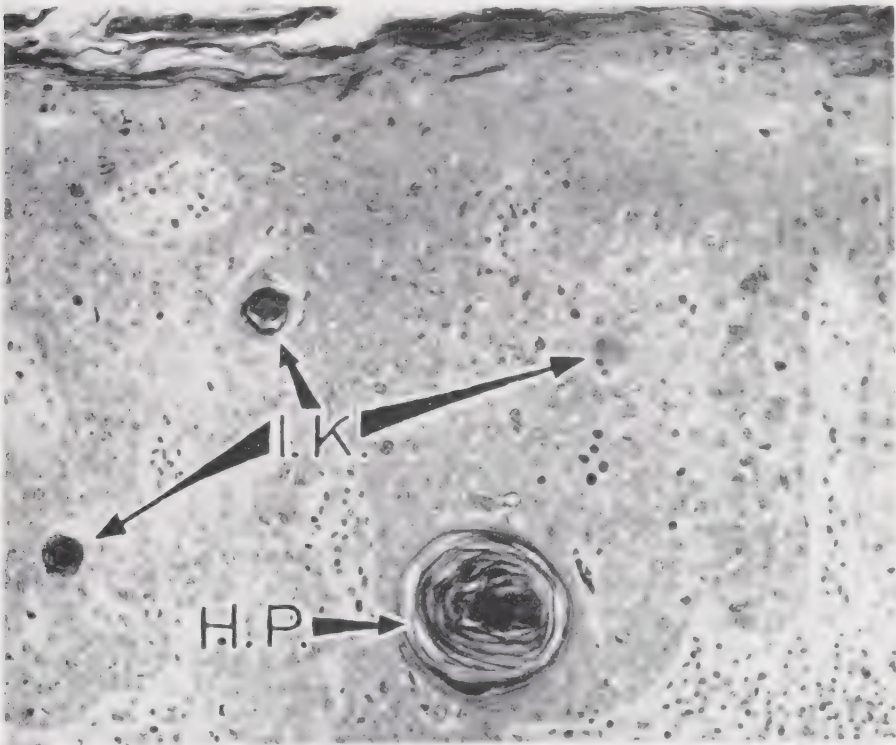


FIG. 165. **Bowen's disease.** In addition to the changes, as described for Figure 164, there are within the stratum malpighii three cells showing "individual cell keratinization" (I.K.), and one horn pearl (H.P.). ($\times 200$)

bridges of these cells are preserved, in contrast with Paget cells, in which they are absent.

A common and, if present, characteristic finding is the presence of individual cell keratinization in the stratum malpighii (Fig. 165). Such keratinized cells are large and round, have a homogeneous and strongly eosinophilic cytoplasm and a large, irregularly shaped, hyperchromatic nucleus. (This individual cell keratinization, which may occur not only in Bowen's disease but also in squamous-cell carcinoma, is often referred to as malignant dyskeratosis in contrast with the benign dyskeratosis that underlies the formation of corps ronds and grains in Darier's disease.) Occasionally, actual horn pearls may occur within the epidermis.

The upper dermis usually shows a moderate amount of inflammatory infiltration composed chiefly of lymphocytes and plasma cells.

As already stated, in true Bowen's disease the basal layer is intact. However, in some cases the basal layer ultimately is broken through and a true invasive squamous-cell carcinoma results. This may occur at first in only one or a few areas. In order not to miss such areas, it is advisable to examine representative sections throughout the entire tissue block. As soon as the invasion of the dermis occurs, the prognosis changes. As long as Bowen's disease remains in the true, intra-epidermal stage, metastases do not occur. However, when invasion of the dermis has occurred, the likelihood of metastases is rather great. This is due to the fact that if Bowen's disease changes into an invasive carcinoma, it usually is Grade II or even Grade III, with considerable atypicality of the cells and little tendency to keratinization (Kuznitzky and Jacoby).

Differential Diagnosis. In the differential diagnosis, senile keratosis and arsenical keratosis must be considered. Senile keratosis may resemble Bowen's disease closely but shows less atypicality of the squamous cells. No sharp line of distinction can be drawn between the two conditions. Arsenical keratosis may closely resemble either Bowen's disease or senile keratosis but shows, as a rule, more vacuolization of the squamous cells than these two diseases.

ERYTHROPLASIA OF QUEYRAT

Erythroplasia of Queyrat usually occurs on the glans penis but may be seen occasionally on the prepuce, the vulva or the oral mucosa. The lesion, usually single, consists of a well-defined area with a brilliant red, velvety surface and little or no infiltration.

Histopathology. Erythroplasia represents an intra-epithelial squamous-cell carcinoma of the mucous membranes and as such is analogous to Bowen's disease of the skin (Pautrier). Progression into

invading squamous-cell carcinoma usually occurs sooner than with Bowen's disease of the skin (Sulzberger and Satenstein; McDaniel and Mason; Pautrier).

Differential Diagnosis. Sachs and Sachs as well as Zoon recently have described cases in which the clinical appearance was identical with that of erythroplasia of Queyrat but in which histologic examination revealed no malignant changes in the epidermis. Instead, the dermis contained an inflammatory infiltrate composed predominantly of plasma cells. Zoon has suggested the diagnostic term "balanoposthitis chronica circumscripta" for these cases. Because the two diseases are indistinguishable on clinical grounds, it is evident that a diagnosis of erythroplasia of Queyrat always requires histologic confirmation.

PAGET'S DISEASE

Paget's disease of the nipple occurs, as a rule, on and around the nipples of women; a few instances of its occurrence on the male breast have been described (Rubenstein). The lesion is always unilateral. Extramammary Paget's disease, which is uncommon, occurs on or near the male and the female genitals, in the perianal region and in the axillae.

The lesion of Paget's disease consists of a sharply defined, slightly infiltrated area of dusky erythema showing scaling, oozing and crusting. If located on the breast, the process begins in the nipple or the areola of the breast and slowly extends to the surrounding skin. There may or may not be retraction of the nipple.

Histopathology. For many years, Paget's disease of the nipple was thought to begin in the skin as a precancerous lesion that later became malignant and then invaded the mammary gland. It is now generally accepted that Paget's disease of the nipple is a cancer from the outset and that the initial lesion is a carcinoma in situ, arising in one or more mammary ducts near their outlets. The primary duct cancer extends from the site of origin downward to the epithelium lining the acini and upward and outward to the epidermis, where it causes the cutaneous lesion. Thus, the tumor cells present in the epidermis, often referred to as Paget cells, are ductal and not epidermal cells (Pautrier; Fraser; Muir; Inglis). At a later stage, the cancer breaks through the wall of a duct or acinus and infiltrates the connective tissue of the breast.

A carcinoma has been found in the mammary ducts in nearly all cases of Paget's disease, and in the mammary glands in most cases. In the few cases where no carcinoma was found in the breast, the underlying ductal carcinoma may have been overlooked because in the

ducts the carcinoma may undergo considerable regression with resultant sclerosis and calcification of the involved ducts (Marx).

Histologic examination of the epidermis reveals in early lesions acanthosis with elongation of the rete ridges; and in older lesions

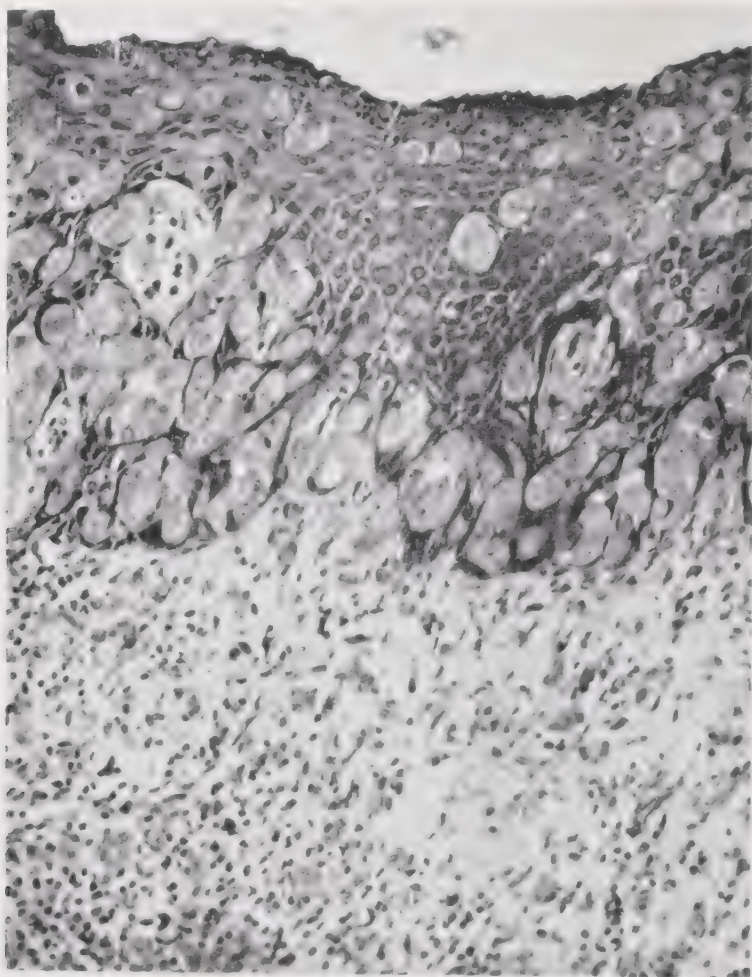


FIG. 166. Paget's disease of the nipple. Low magnification. The epidermis is permeated with numerous Paget cells lying singly and in groups. Note that there is no invasion of the dermis by Paget cells. An inflammatory infiltrate is present in the dermis. ($\times 200$)

thinning and flattening. Paget cells are scattered through the epidermis (Fig. 166). They are large, devoid of prickles and at times appear to lie in clear spaces (Fig. 167). Their cytoplasm stains much lighter than that of the adjacent squamous cells. Their nuclei are large, round and pale-staining. Paget cells usually are most numerous in the basal layer and may cause disorganization of this layer. Invasion of the dermis from the epidermis, however, does not occur.

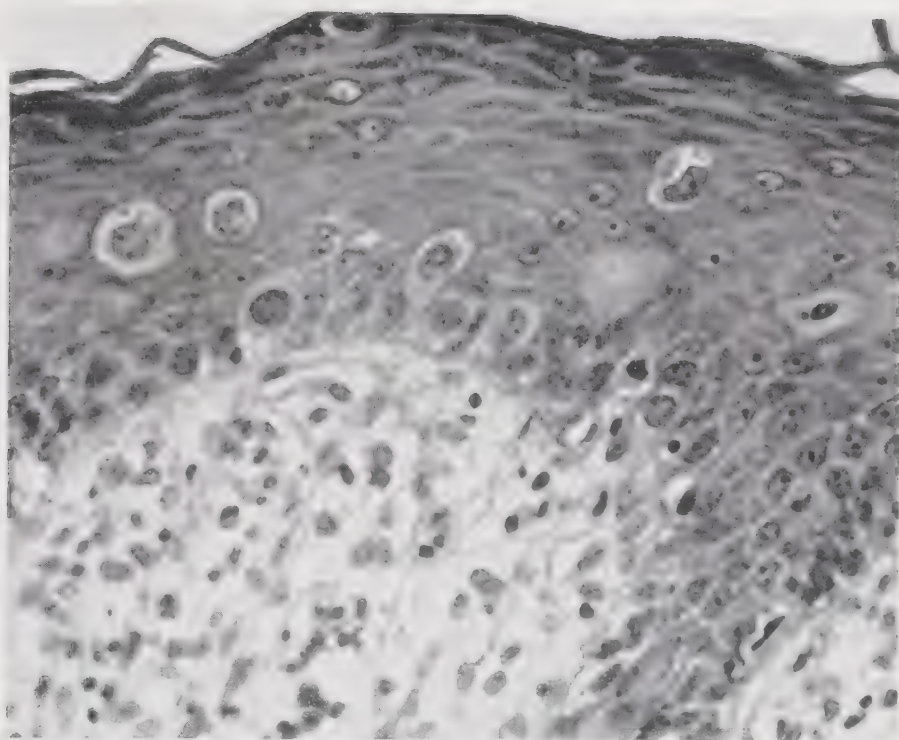


FIG. 167. Paget's disease of the nipple. High magnification. Only a few Paget cells are scattered through the epidermis. They are large, pale-staining and devoid of prickles. ($\times 400$)

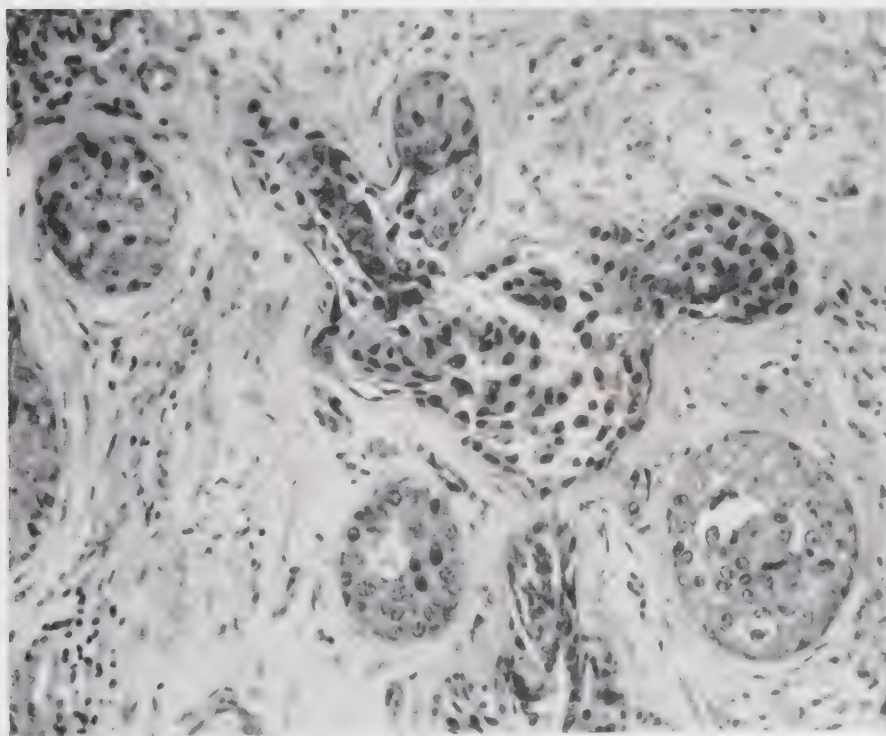


FIG. 168. Paget's disease of the nipple. Intraductal carcinoma is present in the mammary ducts. The carcinoma is confined within the walls of the ducts. ($\times 200$)

In some cases, Paget cells are so numerous throughout the epidermis that the normal squamous cells show signs of injury. They are compressed and deformed and may form only a network, the meshes of which are filled with Paget cells (Fig. 166).

The dermis shows in Paget's disease a moderately severe chronic inflammatory reaction.

Histologic examination of the mammary ducts nearly always shows malignant changes in some of them. At first, the carcinoma is intraductal and the tumor cells are confined within the walls of the ducts (so-called comedo carcinoma) (Fig. 168). Ultimately, the tumor cells invade the connective tissue. From then on, lymphatic spread and metastases occur.

EXTRAMAMMARY PAGET'S DISEASE, as a rule, presents the same epidermal changes as Paget's disease of the nipple, although in lesions located in the perianal region the Paget cells often contain a considerable amount of mucin. In most reported cases, an underlying carcinoma of apocrine ducts and glands has been found (Parsons; Foraker and Miller; Zoon and Gelpke). This is in accordance with the fact that the mammary gland is a modified apocrine gland. The presence of mucin within the Paget cells of some of the cases located in the perianal region may be the result of mucous metaplasia of apocrine glands; but Whimster suggests that the primary cancer may be one of ectopic mucous glands rather than of apocrine glands.

Differential Diagnosis. Paget's disease of the nipple must be differentiated from Bowen's disease. In Bowen's disease, large, vacuolated epidermal cells may also occur, but, in contrast with the Paget cells, they often possess prickles. Furthermore, one observes clumping of nuclei within multinucleated epithelial giant cells and individual cell keratinization in Bowen's disease but never in Paget's disease. In cases in which the Paget cells are concentrated in the lower epidermis, the resemblance to an amelanotic junction nevus or an early malignant melanoma may be very great because in both diseases the characteristic cell is large and vacuolated (Stout). Allen believes that many cases of Paget's disease, and especially of extramammary Paget's disease, are wrongly thus diagnosed and in reality are junction nevi. The most important points of differentiation are: first, the absence of invasion of the dermis by the tumor cells in Paget's disease, and second, the presence of minute amounts of melanin in at least some tumor cells even in apparently amelanotic junction nevi and malignant melanomas. The melanin is best demonstrated by the use of a silver stain. Carrying out of the dopa stain (see page 12) also aids in the differentiation.

2. TUMORS OF THE EPIDERMAL APPENDAGES

NEVUS SEBACEUS (JADASSOHN)

Nevus sebaceus is located most commonly on the scalp or on the face as a single lesion present since birth. It consists of a circum-

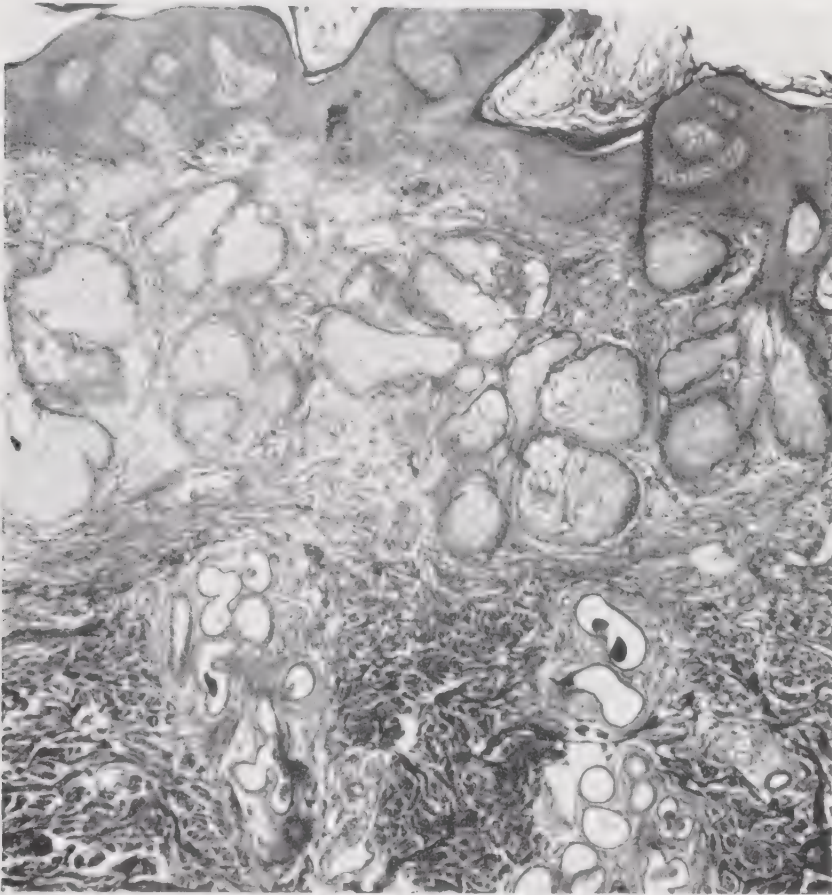


FIG. 169. Nevus sebaceus (Jadassohn). There are hyperkeratosis and papillomatosis. Numerous mature sebaceous glands lie in the upper dermis. In the lower dermis, mature apocrine glands are located. ($\times 50$)

scribed, slightly raised, firm, yellow plaque with a smooth, though furrowed, surface.

Histopathology. The tumor is composed of large numbers of mature or nearly mature sebaceous glands. The overlying epidermis may or may not show hyperkeratosis and papillomatosis. Frequently, apocrine glands have been described as occurring in nevus sebaceus (Robinson; Koch; Pautrier). They are located deep in the dermis beneath the masses of sebaceous gland lobules (Fig. 169). The presence of abortive hair follicles has also been noted on several occasions

(Ostrowski). Koch and Pautrier believe that the frequent presence of apocrine glands is evidence that nevus sebaceus develops from primary epithelial germs. (For a discussion of the primary epithelial germ, see pages 4 and 318.)

The presence of a basal-cell epithelioma within a nevus sebaceus is not uncommon (Fig. 170) (Ostrowski; Robinson; Szodoray; Pautrier;

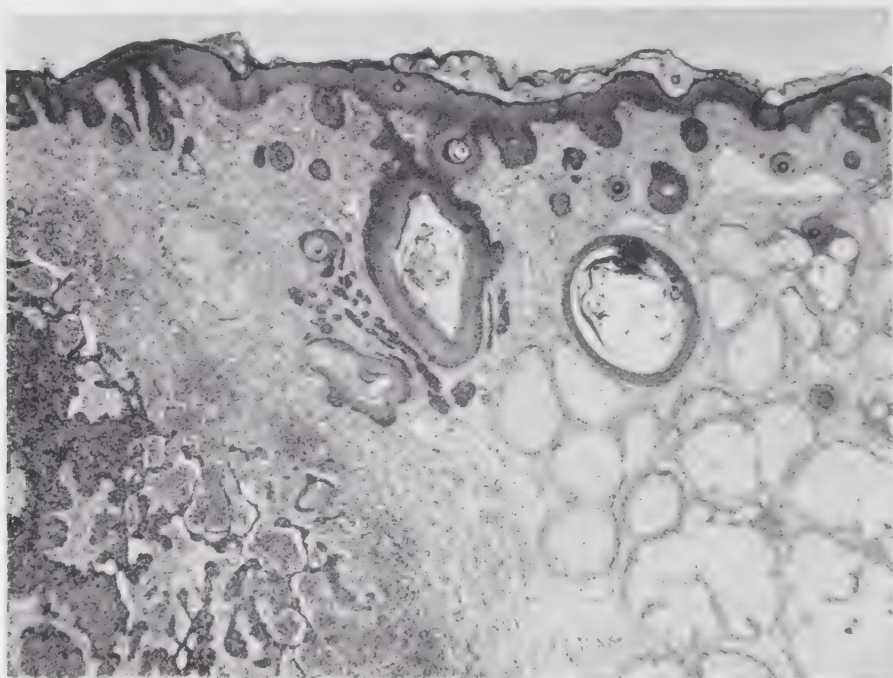


FIG. 170. Nevus sebaceus (Jadassohn) within which a basal-cell epithelioma has arisen. The nevus sebaceus is on the right side, the basal-cell epithelioma on the left. ($\times 25$)

Savatard). In rare instances, a squamous-cell carcinoma may develop from the epidermis overlying the nevus sebaceus (Parkin).

ADENOMA SEBACEUM (PRINGLE) (TUBEROUS SCLEROSIS)

Adenoma sebaceum (Pringle) usually represents only part of a widely disseminated tissue malformation which results in the formation of tumors in both ectodermic and mesodermic structures. Tumors are found, aside from the skin, notably in the brain, the retina, the kidney and the heart. The tumors in the brain, which are referred to as tuberous sclerosis, are gliomas. Those of the retina have the same histologic appearance as the brain tumors (Kveim). The tumors of the heart usually are rhabdomyomas (Pratt-Thomas). Those of the kidney may be angiomas, fibromas, adenomas or mixed tumors; they may become malignant (Butterworth and Wilson).

The cutaneous lesions of adenoma sebaceum (Pringle) occur on the face, particularly in the malar region. They consist of numerous small papules and nodules which are yellowish brown in color and frequently show telangiectases on their surface.

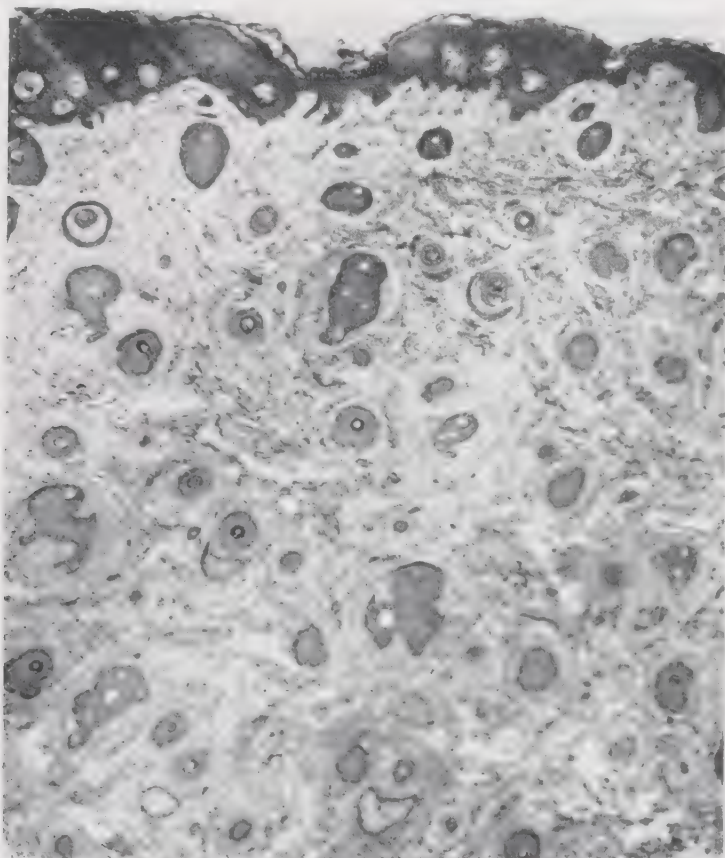


FIG. 171. Adenoma sebaceum (Pringle). Instead of showing excessive development of sebaceous glands, as is usually the case, this lesion shows a large number of immature hair structures. ($\times 50$)

Histopathology. The term adenoma sebaceum is a misnomer. Since the sebaceous structures are not adenomatous but fully or almost fully developed and abnormal merely by their presence in excessive number, the lesion represents an organic nevus, rather than an adenoma (see Table 6, page 319) (Butterworth and Wilson; Moolten).

In addition to excessive development of sebaceous glands, one may find hyperplasia of capillaries or an excessive number of hair structures in the lesions. Occasionally, excessive development of sebaceous glands is absent and, instead, a large number of hair structures are found. Usually, those hair structures are somewhat immature (Fig. 171) (Butterworth and Wilson; Good and Garb).

SENILE SEBACEOUS NEVUS (SENILE SEBACEOUS HYPERPLASIA)

Senile sebaceous nevus occurs on the face, chiefly on the forehead, in persons past middle life, and consists of either one or a few small, yellowish, translucent nodules.

Histopathology. This lesion, like nevus sebaceus (Jadassohn) and adenoma sebaceum (Pringle), is composed of large numbers of mature or nearly mature sebaceous glands. Differentiation of senile sebaceous nevus from the other two lesions on histologic grounds is, therefore, often impossible. In contrast with nevus sebaceus and adenoma sebaceum (Pringle), however, apocrine glands or immature hair follicles are never found.

Senile sebaceous nevus is regarded by some writers as a senile hyperplasia of sebaceous glands (Gilman; Woolhandler and Becker), while others consider it as a delayed, senile organic nevus or hamartoma (Gans). The circumscribed nature of the lesions makes the latter view more likely than the former.

FORDYCE'S DISEASE

In this condition, groups of minute, yellowish, globoid lesions are observed on the vermilion border of the lips or on the oral mucosa.

Histopathology. Fordyce's disease has as pathologic substrate the presence of sebaceous glands in areas where they are normally absent. It thus represents a sebaceous nevus or hamartoma.

Histologic examination reveals groups of mature sebaceous lobules located in the upper dermis. Some lobules lie free in the dermis; others lie at the end of downward proliferations of the overlying epidermis; and still others are connected with the epidermis by true sebaceous ducts (Chambers). However, hairs are never found.

APOCRINE-GLAND NEVUS

Organic nevi composed only of apocrine glands do not occur. Apocrine gland structures, however, frequently are present in nevus sebaceus (Jadassohn) (see page 343) and occasionally in nevus verrucosus (see page 322).

HAIR NEVUS

Purely hair nevi occur, but more commonly they appear in conjunction with other nevoid lesions, for instance, with nevus sebaceus (Jadassohn), nevus verrucosus and nevus pigmentosus. Some cases of adenoma sebaceum (Pringle) are hair nevi rather than sebaceous nevi (see page 345).

SEBACEOUS ADENOMA

An adenoma may be defined as an organoid tumor consisting of circumscribed proliferations of incompletely differentiated glandular structures. If this definition is adhered to, sebaceous adenoma is a very rare tumor. Many tumors described in the literature as sebaceous

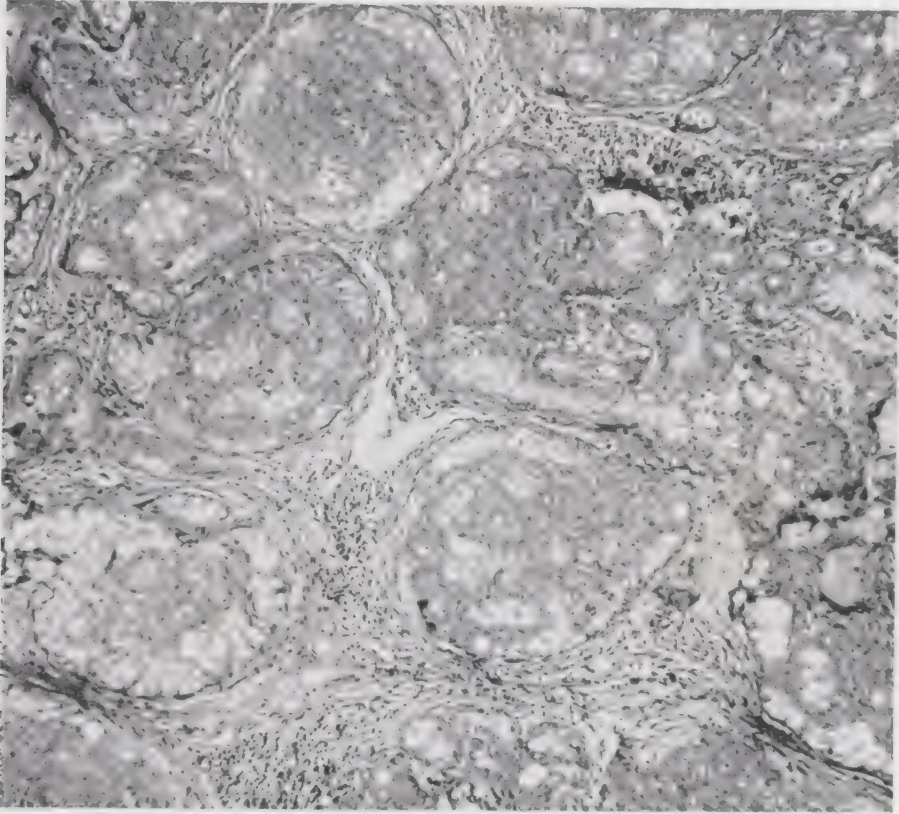


FIG. 172. Sebaceous adenoma. The tumor is composed of lobules which are irregular in size and shape. Two types of cells compose the lobules, generative and sebaceous cells. ($\times 100$)

adenoma are in reality sebaceous nevi. Examples of sebaceous adenoma have been described by Reitmann, Pautrier, Woolhandler and Becker, and Lever, among others.

Sebaceous adenoma occurs as a smooth, firm, round, elevated, often slightly pedunculated, tumor. In most reported cases, the lesion was solitary, located on the face or the scalp, and measured less than 1 cm. in diameter.

Histopathology. On histologic examination, the tumor is sharply demarcated from the surrounding tissue and is usually surrounded by a connective-tissue capsule. It is composed of lobules which are irregular in size and shape (Fig. 172). Two types of cells are present

in the lobules. The cells of the first type are identical with the cells present at the periphery of normal sebaceous glands and resemble the cells of which basal-cell epitheliomas are composed. They have

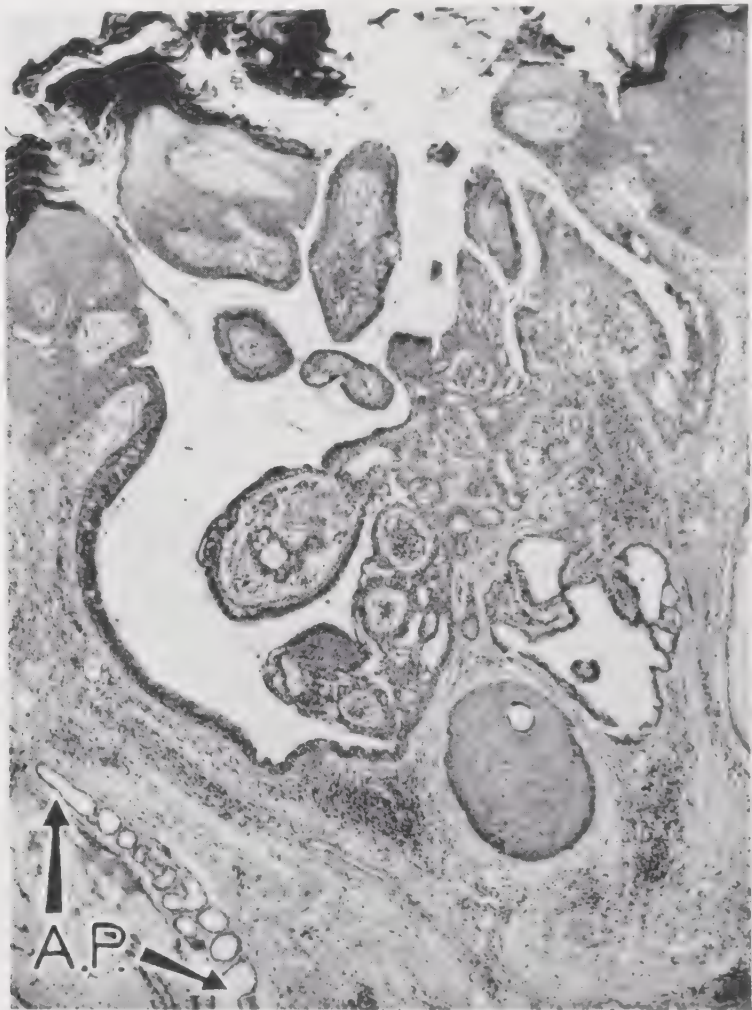


FIG. 173. Syringocystadenoma papilliferum. Low magnification. A cystic invagination extends downward from the epidermis. Numerous villuslike projections extend into the lumen of the cystic invagination. A group of apocrine glands (A.P.) is present in the left lower corner. ($\times 50$)

been called generative cells by Grynfeldt (see page 17). The cells of the second type are mature sebaceous cells. They have developed from the generative cells. In addition, there are cells in a transitional stage of differentiation. The distribution of the generative and the sebaceous cells within the lobules varies. Some lobules contain predominantly generative cells and thus resemble basal-cell epithelioma. Other lobules contain mainly sebaceous cells and resemble mature

sebaceous lobules. In most lobules, however, the two types of cells occur in approximately equal proportions, often arranged in such a way that groups of sebaceous cells are surrounded by generative cells. Larger lobules may contain, in their center, cystic spaces formed by the decomposition of mature sebaceous cells.

Fat stains reveal the presence of fat in the sebaceous and transitional cells and in the cystic spaces.

SYRINGOCYSTADENOMA PAPILLIFERUM (NEVUS SYRINGOCYSTADENOMATOSUS PAPILLIFERUS)

This tumor represents an apocrine-gland adenoma with differentiation predominantly toward apocrine ducts in contrast with hidradenoma papilliferum in which differentiation is directed predominantly toward apocrine glands.

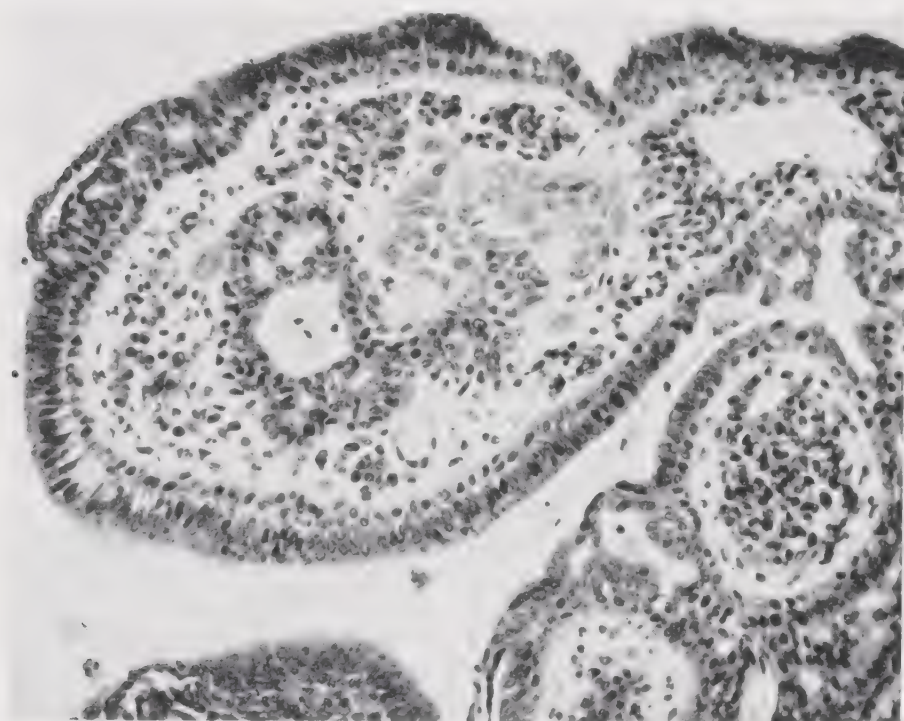


FIG. 174. *Syringocystadenoma papilliferum*. High magnification of Figure 173. The villi are lined by two rows of cells. The outer row is composed of small, cuboidal cells (myo-epithelial cells), the inner row of high, cylindrical cells (secretory cells of apocrine glands). ($\times 200$)

Clinically, syringocystadenoma papilliferum occurs usually as a single, verrucous plaque, located most commonly on the scalp. Scattered through the plaque are areas of crusting. Occasionally, tiny cysts can be recognized.

Histopathology. The epidermis shows acanthosis and papillomatosis. Cystic invaginations extend downward from the epidermis (Fig. 173). These invaginations represent greatly dilated apocrine ducts.

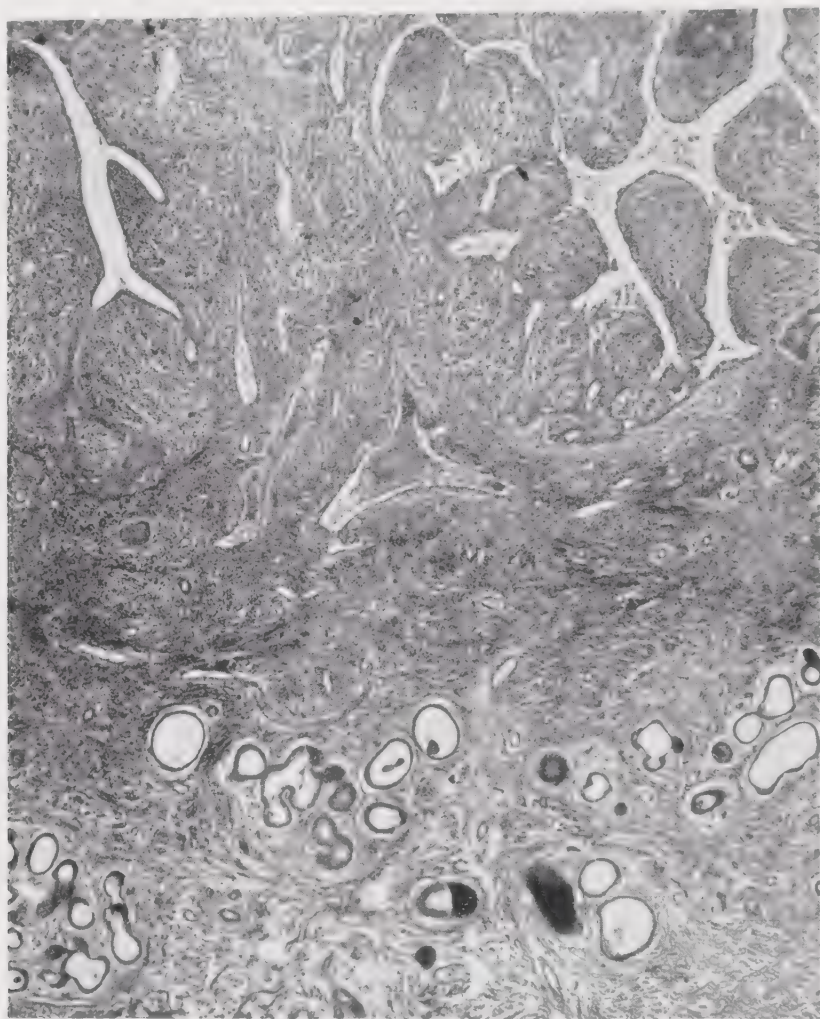


FIG. 175. *Syringocystadenoma papilliferum*. Low magnification. In the upper dermis, there are several cystic invaginations filled with villuslike projections. A marked inflammatory infiltrate containing many plasma cells is present around the cystic invaginations. The lower dermis contains numerous apocrine glands. ($\times 50$)

Numerous villuslike projections extend into the lumina of the invaginations. The cystic invaginations, as well as the villi, are lined by two rows of cells (Fig. 174). The outer row is composed of small cuboidal cells with deeply staining nuclei. These cells are immature myo-epithelial cells. The inner row is composed of high, cylindrical cells which have large, oval, pale-staining nuclei and may show evi-

dence of active secretion. These cells represent secretory cells. Cellular debris is found in the lumina.

Beneath the cystic invaginations, deep in the dermis, one finds groups of glandular lumens (Fig. 175). Their secretory activity ("decapitation secretion") clearly labels them as apocrine glands (Fig. 176) (Tappeiner; Appel; Grund). Connections of the apocrine glands

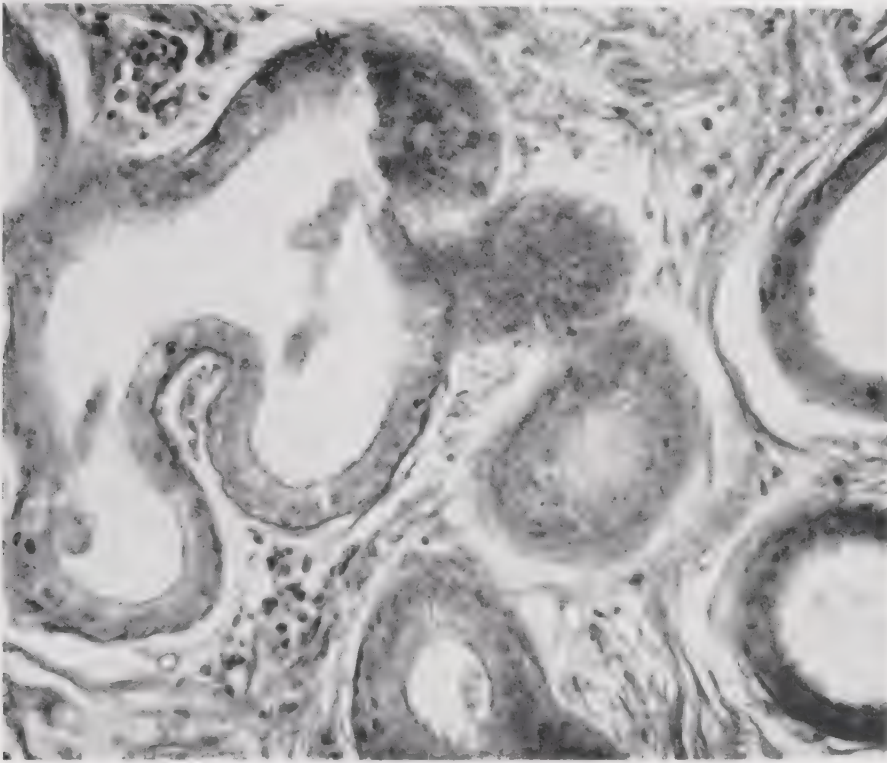


FIG. 176. *Syringocystadenoma papilliferum*. High magnification of the apocrine glands in Figure 175. The secretory cells of the apocrine glands show evidence of active secretion ("decapitation secretion"). ($\times 400$)

with the cystic invaginations in the upper dermis can be traced without difficulty.

In most cases, a dense inflammatory infiltrate is present in the upper dermis, and especially in the villi. This infiltrate contains a large percentage of plasma cells and in some cases is composed almost exclusively of plasma cells.

The association of syringocystadenoma papilliferum with nevus sebaceus (Dörffel; Marcus and Wooldridge; Grund) or with basal-cell epithelioma (Dörffel; Reuterwall) has been noted on several occasions.

Differential Diagnosis. For differentiation from Darier's disease in which villi are also sometimes very prominent, see page 50.

HIDRADENOMA PAPILLIFERUM

This tumor occurs almost exclusively on the labia majora and on the perineum of women as a solitary, intracutaneous lesion covered by normal epidermis. It usually measures only a few millimeters in diameter. Malignant degeneration does not occur.

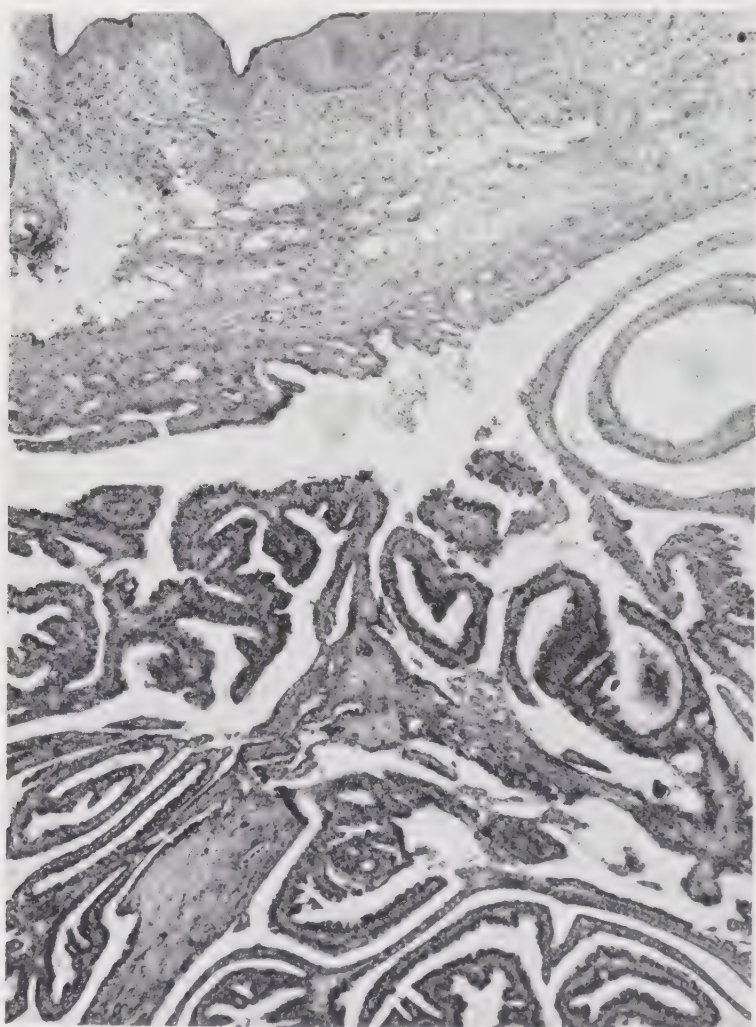


FIG. 177. *Hidradenoma papilliferum*. Low magnification. The tumor consists of a large cystlike lumen into which numerous interlacing villi project. ($\times 50$)

Histopathology. The tumor represents an adenoma of apocrine glands (Anderson; Winer). It is located in the dermis, shows no connection with the epidermis, and is well encapsulated. It is composed of a large, cystlike lumen into which numerous interlacing villi project (Fig. 177). The wall of the cyst as well as the villi are lined usually by a single layer of high cylindrical cells. These cells have a

faintly eosinophilic cytoplasm and a large, oval, pale-staining nucleus and show evidence of active secretion, like apocrine gland cells (Fig. 178). Sometimes, myo-epithelial cells are seen peripheral to the secretory cells, either arranged in a single layer or proliferating irregularly into the interstitial tissue (McDonald).

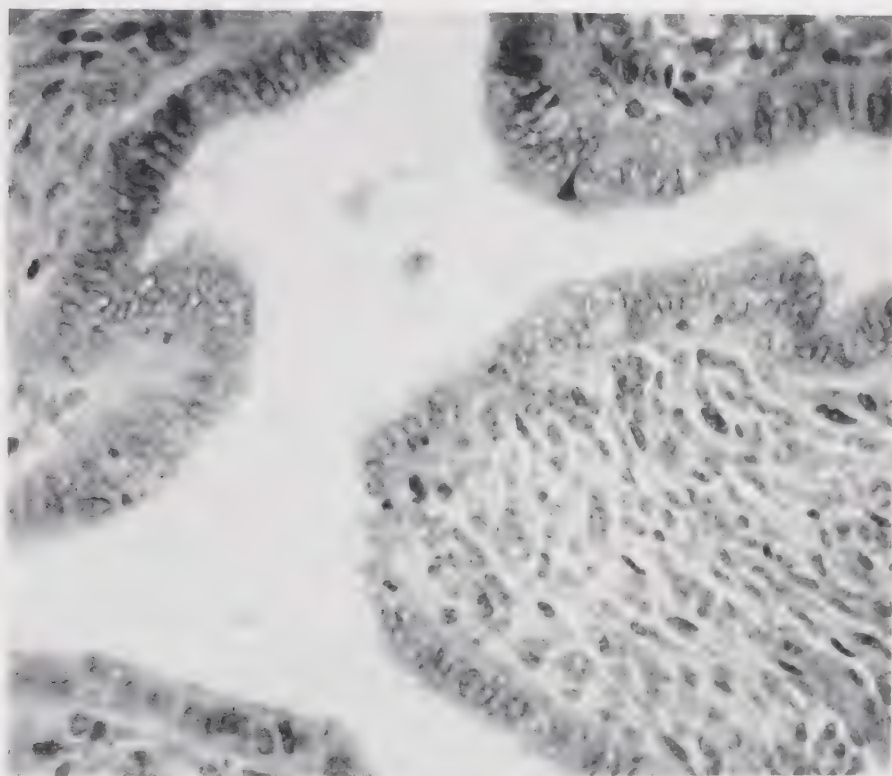


FIG. 178. *Hidradenoma papilliferum*. High magnification of Figure 177. The villi are lined by one layer of high cylindrical cells, which show evidence of active secretion like apocrine glands. ($\times 400$)

Gates, Warren and Warvi have pointed out that hidradenoma papilliferum closely resembles the papillary cystadenomas of the mammary gland. It should be remembered that, phylogenetically, the mammary gland is an apocrine gland.

SEBACEOUS EPITHELIOMA

Clinically, the tumor has no characteristic appearance. Usually, it presents itself as a solitary, small nodule or plaque. It is an uncommon type of tumor. Examples have been described by Grynfeldt; Biberstein; Milian, Périn and Brunel; and Lever.

Histopathology. In degree of differentiation, sebaceous epithelioma stands between sebaceous adenoma, in which there are typical sebaceous lobules, and cystic basal-cell epithelioma, in which there

is but little differentiation toward sebaceous cells. (See Table 6, page 319.) As Loos has put it, sebaceous epithelioma grows like a basal-cell epithelioma but its cells have undergone considerable differentiation toward sebaceous cells.

The tumor is composed of irregularly shaped cell masses which are scattered through the upper dermis (Fig. 179). The majority of cells

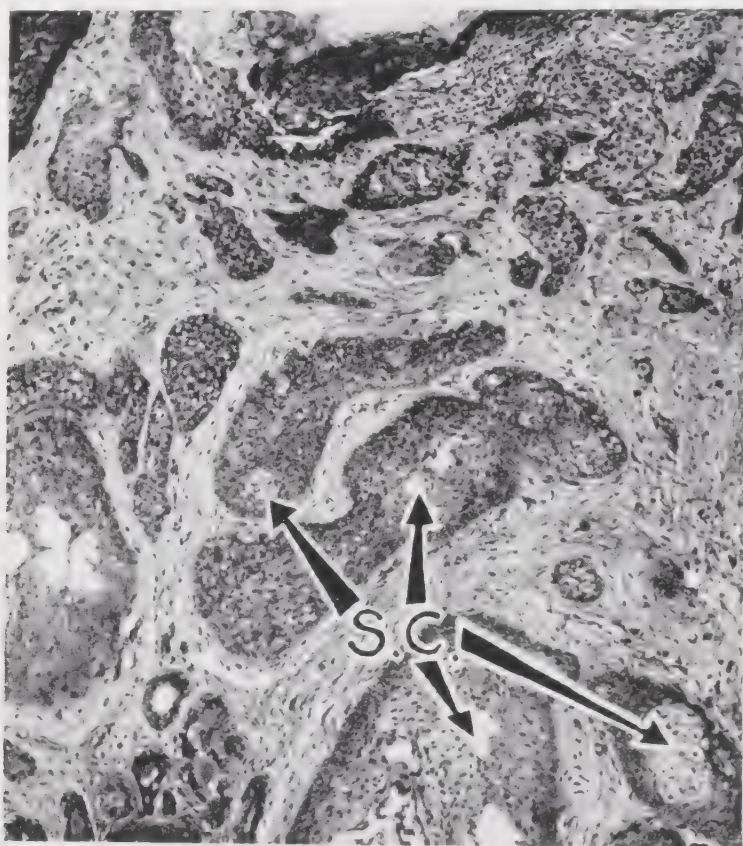


FIG. 179. **Sebaceous epithelioma.** The tumor is composed of irregularly shaped cell masses. The majority of cells are of the same type as in basal-cell epithelioma, but many cells (S.C.) show differentiation toward sebaceous cells. ($\times 100$)

are of the same type as the cells in basal-cell epithelioma. However, a fairly large number are transitional cells showing beginning fatty transformation of their cytoplasm. Groups of mature sebaceous cells lie in the centers of the cell masses. Cysts formed by the disintegration of sebaceous cells may or may not be present in the center of some of the tumor masses.

SYRINGOMA

Three types of apocrine epitheliomas occur: syringoma, cylindroma and myo-epithelioma (see Table 6). While in syringoma

differentiation is directed mainly toward apocrine duct cells, differentiation in cylindroma is directed mainly toward apocrine gland cells, and in myo-epithelioma mainly toward apocrine myo-epithelial cells.

Syringoma occurs predominantly in women and develops at puberty. Hundreds of small, soft, slightly yellowish nodules, the size

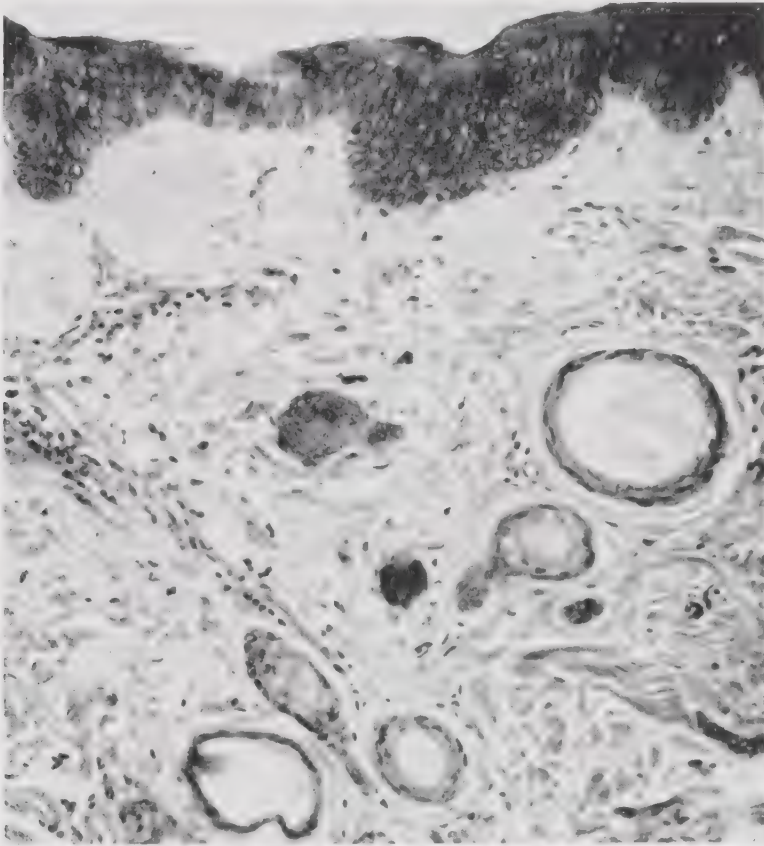


FIG. 180. Syringoma. The dermis contains several small cystic ducts. The walls of most ducts are lined by two rows of epithelial cells. Colloidal material fills the lumina. Two of the ducts have comma-like tails giving them the appearance of tadpoles. ($\times 200$)

of a pinhead, are found around the eyelids, on the chest, on the abdomen and on the anterior aspects of the thighs, but occasionally also elsewhere on the skin.

Histopathology. The dermis contains numerous, small, cystic ducts (Fig. 180). The walls of the ducts are lined usually by two rows of epithelial cells. In most instances, these cells are flat and appear as if compressed. Occasionally, however, the cells of the inner row show evidence of active secretion and resemble apocrine gland cells (Weid-

man and Besancon; Riehl; Homma and Escher; Wendlberger). The lumina of the ducts are filled with a colloidal material. Some of the cystic ducts possess small, comma-like tails of epithelial cells, giving them the appearance of tadpoles. In addition, there are solid strands of epithelial cells independent of the ducts. The cells composing the

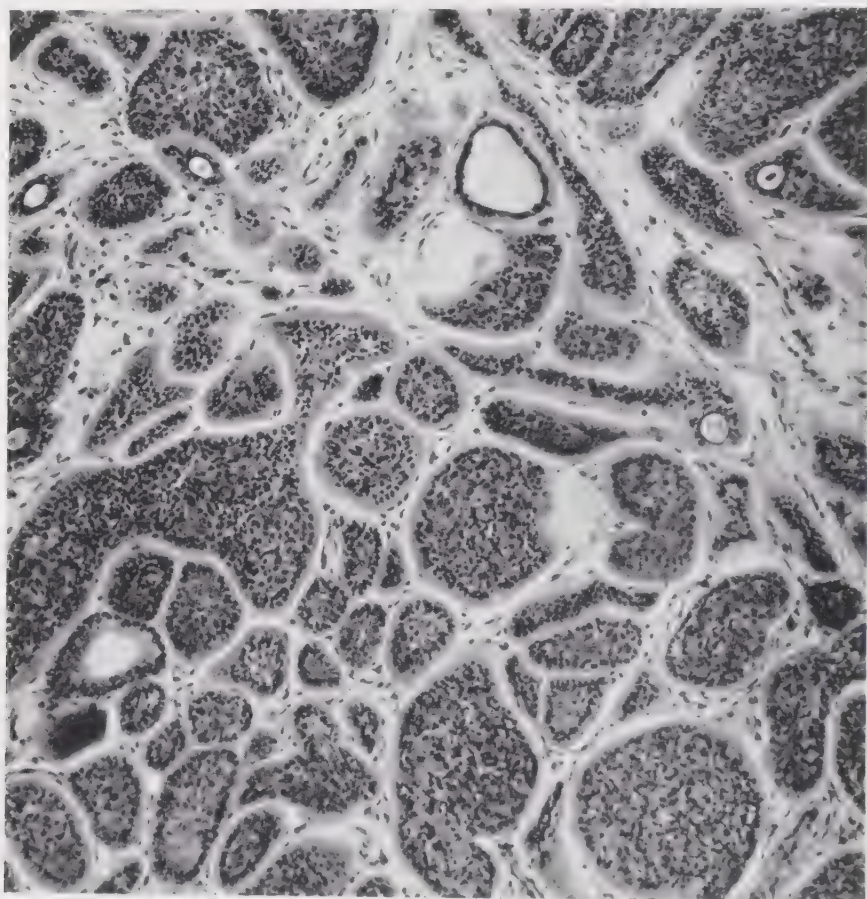


FIG. 181. **Cylindroma.** Low magnification. The tumor is composed of various-sized islands of epithelial cells. The islands are surrounded by a hyaline membrane. Several of the islands in the left lower quadrant contain droplets of hyalin. ($\times 75$)

solid strands have the same appearance as the cells in basal-cell epithelioma. Rudimentary hair structures are found occasionally in the lesions (Fischer).

Several authors have reported the simultaneous occurrence of syringoma and tricho-epithelioma (epithelioma adenoides cysticum) in the same patient (McDonagh; Weidman and Besancon) and even in the same lesion (Ingels; Lever).

The reasons given by various authors for the apocrine genesis of syringoma are: (1) the presence of active secretion (Weidman and

Besancon; Riehl; Homma and Escher; Wendlberger); (2) its simultaneous occurrence with rudimentary hair structures or with trichoepithelioma, a tumor of hair structures (Fischer; Lever); (3) its appearance at puberty when apocrine glands first begin to function (Kyrle; Wendlberger) and (4) the prevalence of the lesions in areas of the skin where apocrine glands occur or used to occur phylogenetically (Wendlberger).

CYLINDROMA

This disorder, which is often hereditary, is characterized by the presence of numerous, rounded, smooth tumors of various sizes on

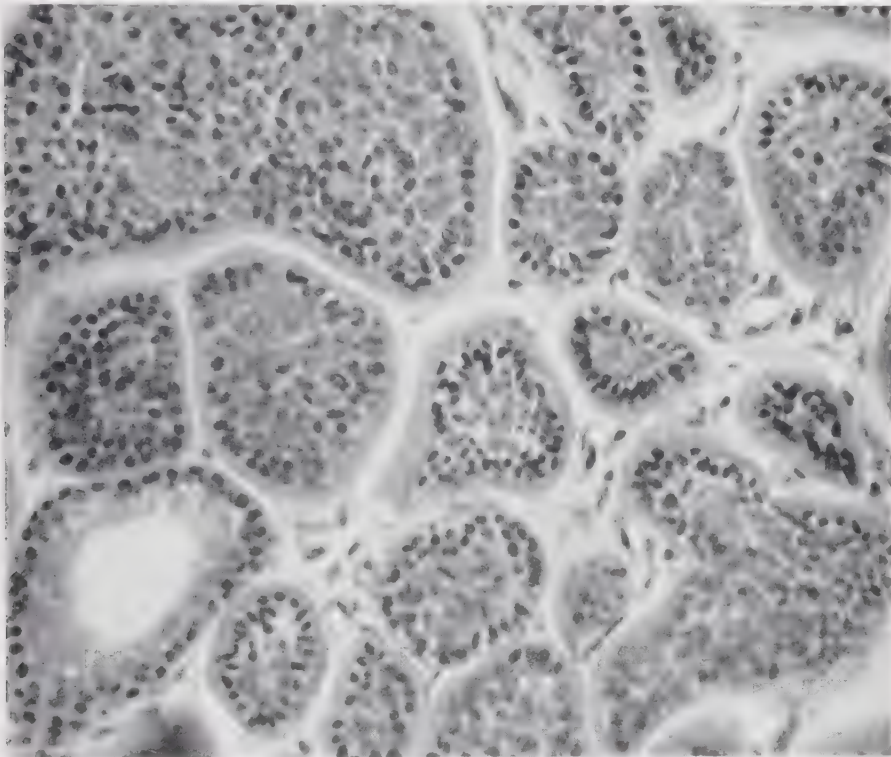


FIG. 182. Cylindroma. High magnification of Figure 181. Two types of epithelial cells compose the islands. There are cells with small, dark nuclei (myo-epithelial cells) and cells with large, pale nuclei (secretory cells). In the lower left corner, there is a glandular lumen lined by two rows of cells. The cells of the inner row show active secretion like apocrine-gland cells. ($\times 200$)

the scalp. Occasionally, a few tumors are present also on the face and the upper trunk. The lesions begin to appear in early adulthood and increase in number and size throughout life. They vary in size from a few millimeters to several centimeters and, by their arrangement in groups, resemble bunches of grapes or tomatoes. The tumors

may cover the entire scalp like a turban. For this reason, they are referred to occasionally as turban tumors.

Histopathology. The tumors are composed of numerous, variously sized islands of epithelial cells. These islands are surrounded by a hyaline membrane. In addition, droplets of hyalin are present in some of the islands (Fig. 181). Two types of cells compose the islands (Stillians; Savatard; Zakon; Lever). Cells with large, oval, light-staining nuclei lie in the centers of the islands, while cells with small, round, dark-staining nuclei are present in palisade arrangement at the periphery of the islands and also scattered between the cells of the first type (Fig. 182). The cells of the first type may be regarded as cells differentiating toward secretory cells; those of the second type as cells differentiating toward myo-epithelial cells of apocrine glands. The secretory cells always outnumber the myo-epithelial cells. The hyalin which is present around and within the islands appears to be produced by the myo-epithelial cells, since it is always found in apposition to them. It is particularly well demonstrated by staining with methylene blue.

In some cases, a thorough inspection of the histologic sections will reveal the presence of a few glandular lumina lined by two layers of cells, an inner actively secreting layer and an outer myo-epithelial layer (Stillians; Lever) (Fig. 182). These glandular structures strongly resemble apocrine glands.

Several authors have observed connections of the tumor masses with hair follicles (Watanabe; Stillians; Schlammdinger). The simultaneous presence of cylindroma and tricho-epithelioma (epithelioma adenoides cysticum) in the same patient has been observed repeatedly (Watanabe; Schlammdinger; Schuermann and Weber; Savatard). Cylindromas nearly always remain benign. Two cases, however, are on record in which malignant degeneration of the tumors occurred, with metastases to the lymph nodes in one case (Lausecker), and to internal organs as well in the other (Luger). The areas of malignant degeneration showed in the cell lobules polymorphism of the nuclei, numerous mitotic figures, loss of the hyaline sheath, loss of palisading at the periphery and invasion into the surrounding stroma.

The histogenesis of cylindroma is not yet clearly established. Some authors (Coenen; Davies) regard it as a sweat-gland tumor, others (Watanabe; Stillians; Schlammdinger) as a hair-follicle tumor, and still others (Balog; Schuermann and Weber) as an apocrine tumor. In favor of the apocrine genesis of cylindroma are: (1) the presence of two types of cells, namely, secretory and myo-epithelial cells; (2) the occasional presence of actively secreting glandular lumina;

and (3) its simultaneous occurrence with tricho-epithelioma, a tumor of hair structures.

MYO-EPITHELIOMA (MYO-EPITHELIAL SWEAT GLAND TUMOR)

Myo-epithelioma occurs, as a rule, as a solitary tumor; occasionally, however, several lesions are present. The tumors present themselves

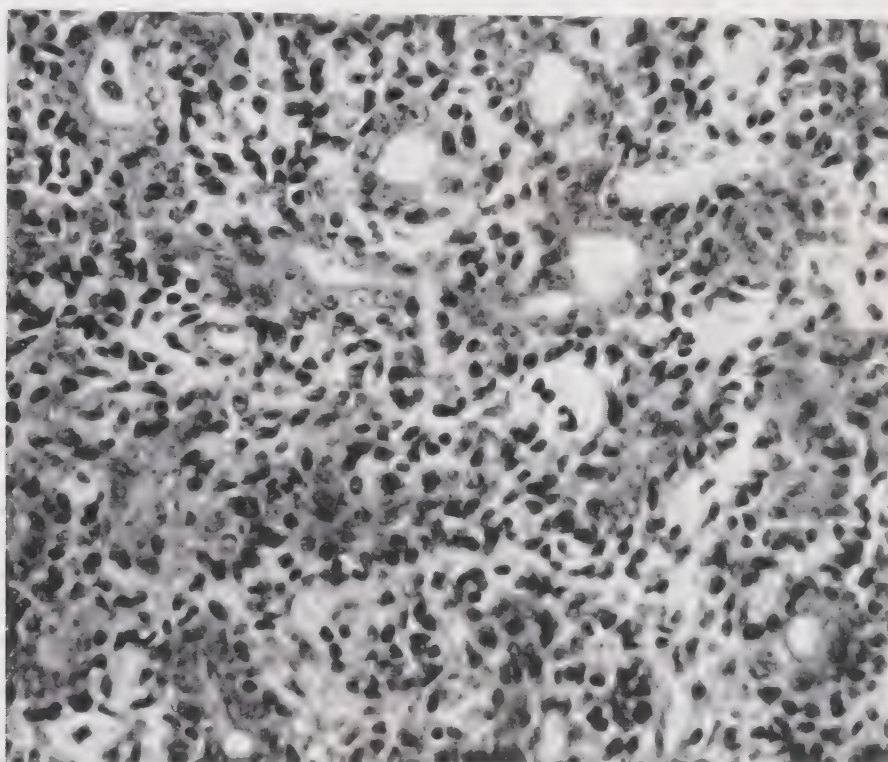


FIG. 183. Myo-epithelioma. The epithelial cells are arranged in intermingling bands. Two types of cells can be seen. Secretory cells lie in the center of the bands and tend to be arranged around lumina. Myo-epithelial cells lie at the periphery of the bands. ($\times 400$)

as firm, intracutaneous nodules and usually measure between 0.5 and 2 cm. in diameter, although they may be larger. The overlying skin is either normal or shows slight erythema. Myo-epithelioma is a rather uncommon tumor. Examples have been described by Sheldon, Balog, Hartz, and Lever.

Histopathology. Histologic examination reveals a sharply circumscribed, usually encapsulated, essentially solid tumor. The epithelial cells of the tumor are arranged usually in intertwining bands, but occasionally in lobular masses. The same two types of cells are present as in cylindroma, namely, secretory and myo-epithelial cells; but,

in contrast with cylindroma, the majority of cells are myo-epithelial cells. The secretory cells lie in groups and frequently are arranged around lumina which are usually small.

In myo-epitheliomas with bandlike arrangement of the epithelial cells, the secretory cells are located in the center and the myo-epi-

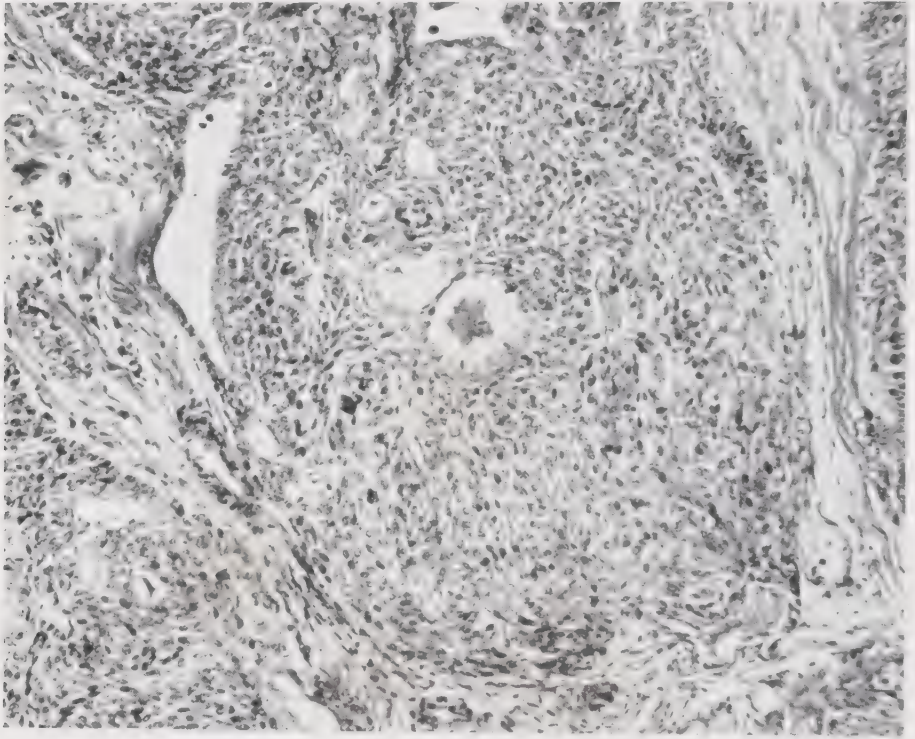


FIG. 184. **Myo-epithelioma.** The epithelial cells are arranged in lobules. The lobule shown is composed largely of myo-epithelial cells, but lumina lined with secretory cells are scattered through the lobule. ($\times 200$)

thelial cells at the periphery of either tubules or solid bands (Fig. 183). The myo-epithelial cells may be seen proliferating irregularly into the stroma. In myo-epitheliomas with lobular arrangement, the lobules are composed largely of myo-epithelial cells, but throughout the lobules one finds lumina lined with secretory cells (Fig. 184).

Some of the tumors possess a considerable amount of stroma of hyaline appearance and thus resemble the so-called mixed tumors of the salivary gland type.

MIXED TUMOR OF THE SKIN

Mixed tumors of the salivary-gland type occasionally have been described as occurring in the skin (Hirsch; Highman; Morehead;

Lennox, Pearse and Richards). Their clinical appearance is the same as that of myo-epithelioma.

Histopathology. Mixed tumors of the skin show epithelial cells arranged in nests and strands as well as around small lumina (Fig. 185). Either one or two layers of epithelial cells are present around the lumina. In addition, epithelial cells may be seen proliferating irregularly from the lumina into the stroma. The majority of epi-

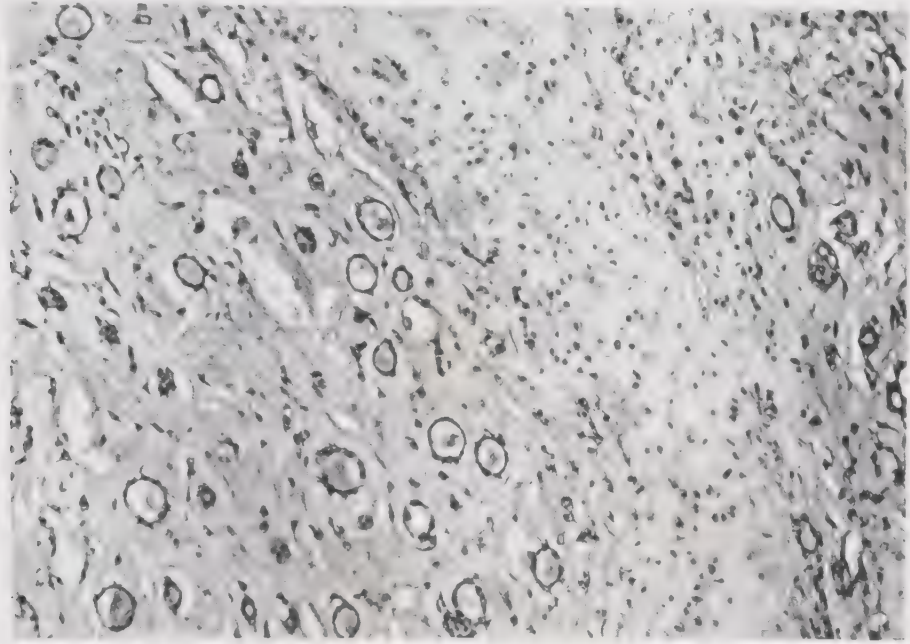


FIG. 185. Mixed tumor of the skin. Epithelial cells lie arranged around small tubular lumina and scattered through the stroma. The stroma shows mucoid and hyaline degeneration. ($\times 100$)

thelial cells are spindle-shaped and resemble myo-epithelial cells (Morehead). Those located around lumina have the appearance of glandular cells. The stroma usually is abundant and shows hyaline and mucoid degeneration.

Some authors regard the mixed tumors of the skin as of sweat-gland origin (Hirsch; Lennox, Pearse and Richards). It is the author's belief that most, if not all, mixed tumors of the skin represent myo-epitheliomas. They differ from myo-epitheliomas only by showing a greater amount of stroma and more marked degenerative changes in the stroma.

CLEAR-CELL MYO-EPITHELIOMA

The clinical appearance of this tumor is that of a solitary nodule usually covered by intact skin but occasionally discharging serous material.

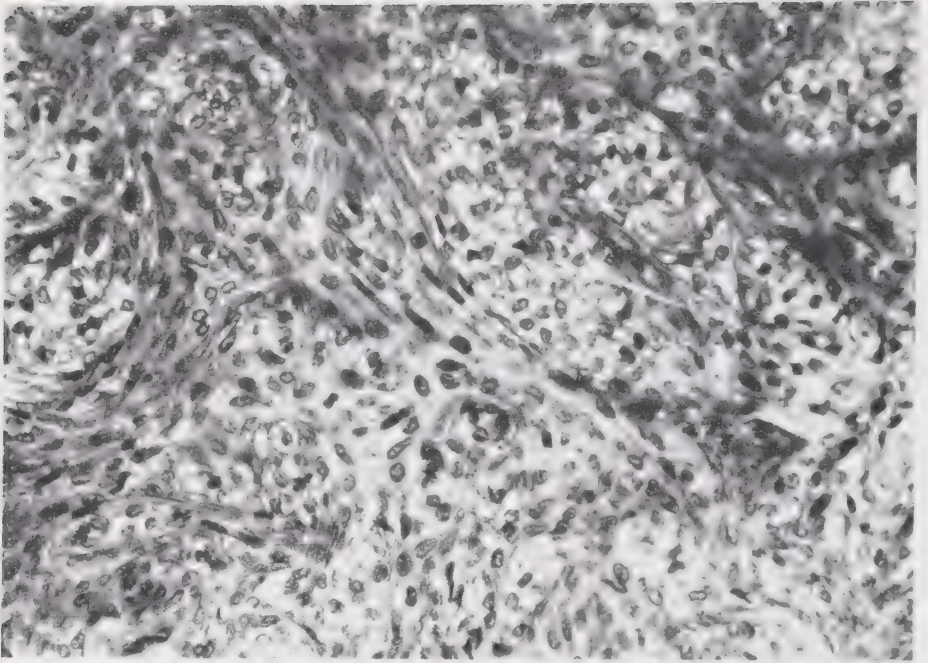


FIG. 186. Clear-cell myo-epithelioma. The tumor is composed of two types of cells: fusiform myo-epithelial cells and cuboidal "clear cells." ($\times 200$)

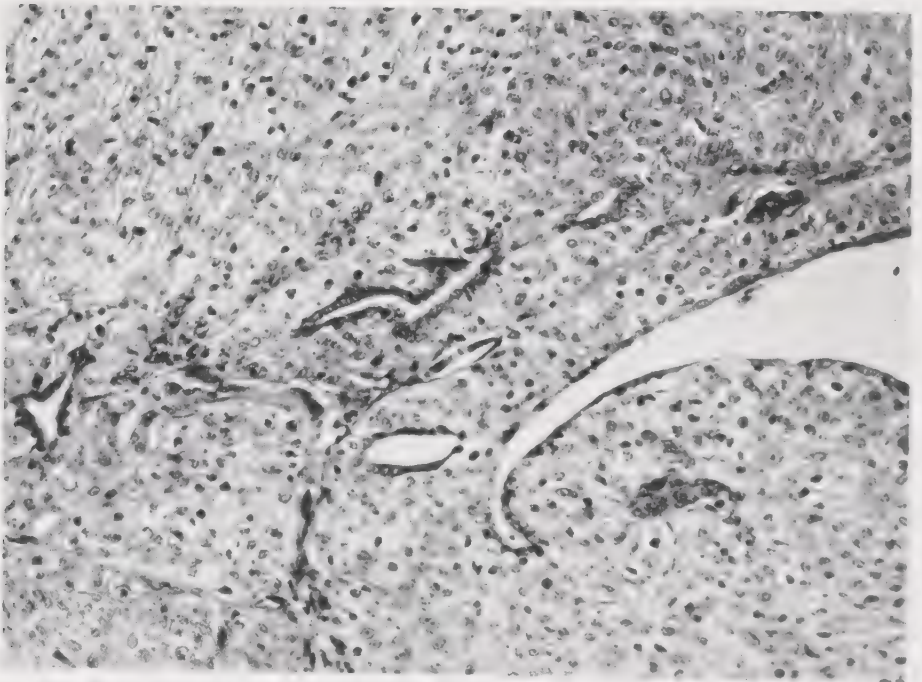


FIG. 187. Clear-cell myo-epithelioma. There are numerous clear cells and, in addition, tubular lumina lined by a single layer of secretory cells. ($\times 200$)

Histopathology. The tumor has a lobular structure. Two types of epithelial cells can be recognized: fusiform, myo-epithelial cells with deeply basophilic nuclei, and "clear cells" which are cuboidal, have a distinct cellular membrane, very clear cytoplasm and a round nucleus (Fig. 186). The clear cells seem to develop from the myo-epithelial cells (Lever and Castleman). Varying amounts of glycogen are present in the clear cells. In some tumors, there are groups of keratinized cells, cysts and glandular structures. The glandular structures are tubular and their lining cells often show "decapitation secretion" as observed in apocrine glands (Fig. 187).

While Lever and Castleman regard this type of tumor as a variant of myo-epithelioma, Liu, because of the presence of glycogen, thought that it was derived from the outer hair sheath which normally contains abundant amounts of glycogen. However, glycogen is found so commonly in young cells and in tumors that its presence cannot be considered as a reliable criterion for the histogenetic classification of neoplasms.

TRICHO-EPITHELIOMA (EPITHELIOMA ADENOIDES CYSTICUM, MULTIPLE BENIGN CYSTIC EPITHELIOMA)

The name tricho-epithelioma is preferable to the other names listed above because it indicates that differentiation in this tumor is directed toward hair structures.

The disorder begins, as a rule, at the age of puberty and is frequently hereditary. It is characterized by the presence of numerous, pinhead- to pea-sized, rounded, yellowish or pink nodules on the face and, occasionally, on the upper trunk. A few telangiectatic vessels are often present on the surface of the larger lesions. Occasionally, one or several lesions become ulcerated because of change into a basal-cell epithelioma.

Histopathology. On histologic examination, tricho-epithelioma appears as a well-circumscribed tumor. Horn cysts represent the characteristic lesion. They consist of a fully keratinized center surrounded by a shell of flattened "basal cells" without prickles (Fig. 188). The keratinization in the horn cysts is abrupt and complete, not gradual and incomplete as in the horn pearls of squamous-cell carcinoma. This process corresponds to the abrupt development of the horn cells of the hair from the hair matrix cells (which are also cells without prickles). It may be concluded, therefore, that the cells surrounding the horn cysts are hair-matrix cells and that the horn cysts represent attempts at hair-shaft formation (Lever). Occasionally, one sees prickle cells around some of the horn cysts. They represent outer hair-sheath cells. Since the outer hair sheath develops from

prickle cells at a time when the hair germ has already advanced to a rather high stage of differentiation, the presence of prickle cells around the horn cysts is evidence of rather high differentiation.

In addition to horn cysts, irregularly shaped islands and intertwining strands composed of "basal cells" are present. Such areas are indistinguishable from basal-cell epithelioma (Goldman). Abortive



FIG. 188. **Tricho-epithelioma.** The tumor contains numerous horn cysts. In the center, near the epidermis, two rudimentary hairs can be seen. ($\times 100$)

hair papillae and hair shafts are seen occasionally. Since hair papillae contain a high concentration of alkaline phosphatase (Hardy) their presence can be well demonstrated by the use of the Gomory stain for alkaline phosphatase. Calcification of the horn cysts may occur and evoke a foreign-body giant-cell reaction in the adjacent connective tissue.

Tumors histologically in an intermediate stage between tricho-epithelioma and basal-cell epithelioma occur (Summerill and Hutton; Traenkle). As just stated, a typical tricho-epithelioma is characterized by circumscribed growth and by the presence of many horn cysts and of "basal-cell" masses; however, basal-cell epithelioma may

also show horn cysts (Fig. 189) (see page 379) and may be circumscribed in growth. Since thus no sharp line of demarcation exists between tricho-epithelioma and basal-cell epithelioma histologically, it may be necessary, in order to arrive at a diagnosis in a given case, to have knowledge of clinical data, such as the number and the distribution of the lesions and the age at which the lesions first ap-



FIG. 189. Basal-cell epithelioma with horn cysts. Histologically, this tumor is in an intermediate stage of differentiation between basal-cell epithelioma and tricho-epithelioma. Clinically, the lesion was a basal-cell epithelioma. ($\times 200$)

peared. The close relation between the two types of tumors is attested further by reports of cases in which one or several of the lesions of tricho-epithelioma, after having persisted as such for many years, developed into ulcers with the histologic picture of basal-cell epithelioma (Adamson; Little; Savatard). This close relationship of the two types of tumors can be explained best by assuming that they have a common genesis from primary epithelial germs (Lever) and that they differ only in the degree of maturity of their cells (Adamson). Since cells of various maturity may occur in the same lesion, one may find in tricho-epithelioma areas consistent with the histologic picture of basal-cell epithelioma and vice versa; also, if active growth occurs in a lesion of tricho-epithelioma, the newly formed cells may

be more embryonal than the older cells and the lesion may grow as a basal-cell epithelioma.

A close relation exists not only between tricho-epithelioma and basal-cell epithelioma, but also between tricho-epithelioma and other types of benign epitheliomas, such as syringoma and cylindroma. Tricho-epithelioma may occur with syringoma or cylindroma in the same patient (see pages 356, 358).

CALCIFYING EPITHELIOMA (MALHERBE)

Calcifying epithelioma is a solitary, hard, deep-seated tumor which is covered by normal skin. It occurs most frequently on the face and

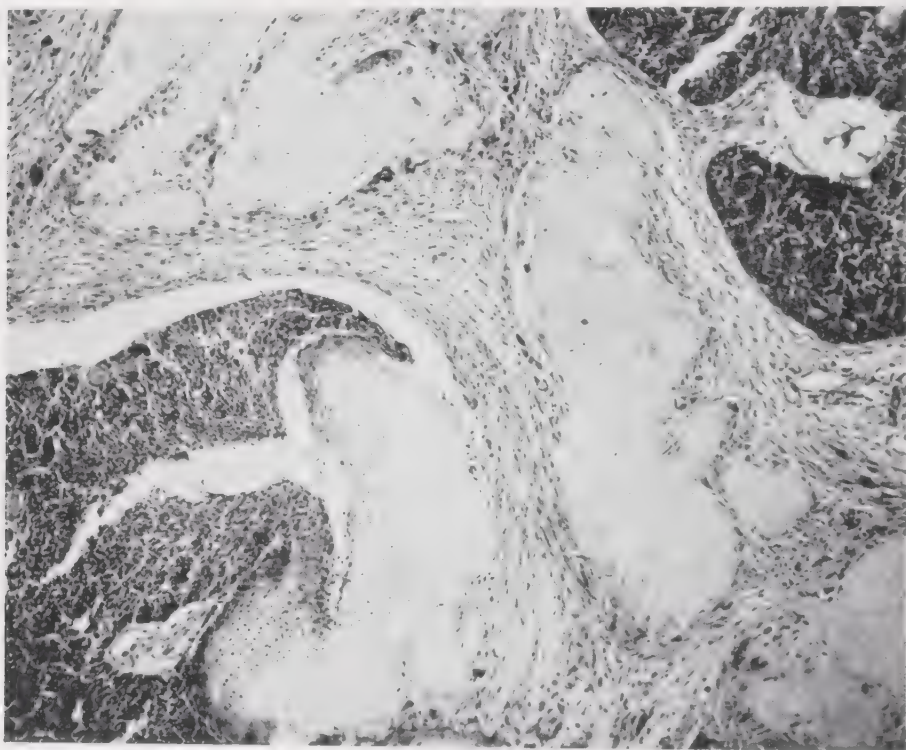


FIG. 190. **Calcifying epithelioma (Malherbe).** The tumor consists of lobules embedded in a connective-tissue stroma. Two types of cells compose the lobules: "basophilic cells" and "shadow cells." The basophilic cells resemble the cells of basal-cell epithelioma. The shadow cells show a central unstained shadow at the site of the nucleus. In the center of the field, one can see transformation of the basophilic cells into shadow cells. The stroma contains numerous foreign-body giant cells. ($\times 100$)

the upper extremities. The size is from 0.5 to 3 or even 5 cm. in diameter.

Histopathology. Calcifying epithelioma is a sharply demarcated, often encapsulated tumor and usually located in the lower dermis

or in the subcutaneous fat. The histologic appearance is characteristic. Embedded in a connective-tissue stroma, variously shaped masses of epithelial cells are present. As a rule, two types of cells—"basophilic cells" and "shadow cells"—compose these masses (Fig. 190). Occasionally, basophilic cells are absent. The basophilic cells greatly resemble the cells of basal-cell epithelioma. They possess



FIG. 191. Calcifying epithelioma (Malherbe). Small and large areas of calcification are present within the lobules of "shadow cells." ($\times 100$)

large, round or elongated, deeply basophilic nuclei and only little cytoplasm, so that the nuclei are densely packed. The cellular borders are often indistinct so that it appears as if the nuclei were embedded in a symplasmic mass. The shadow cells stain pale pink with hematoxylin-eosin. They have a distinct border but take no nuclear staining. Instead, they show a central unstained "shadow" at the site of the nucleus. In some areas, one can see clearly that the shadow cells develop from the basophilic cells (Fig. 190). In tumors of recent origin, numerous areas of basophilic cells are usually present. As the lesion ages, the number of basophilic cells decreases due to their development into shadow cells, and in tumors of long standing few or no basophilic cells remain. In addition to basophilic and shadow

cells, areas of cornification are present. The cornification may occur as sheets of horn cells or as small, round centers of cornification. Sheets of horn cells are found only within the masses of shadow cells, while the small, round centers of cornification may lie within areas of basophilic cells as well as within the masses of shadow cells. In occasional instances, melanin is present within the tumor. The melanin may be located in either the basophilic cells, the shadow cells or the stroma (Turhan and Krainer; Lever and Griesemer).

The stroma of the tumor usually shows a considerable foreign-body giant-cell reaction adjacent to the masses of shadow cells. A frequent but not constant feature is calcification (Fig. 191). The calcium may be present in large sheets replacing the shadow cells or may be present as fine granules within the cytoplasm of shadow cells. Occasionally, ossification of calcified areas takes place (Nicholson; Highman and Ogden). Malignant degeneration does not occur.

Histogenesis. The histogenesis of calcifying epithelioma is not established fully. Originally described by Malherbe and Chenantais as a calcified epithelioma of sebaceous glands, it has been variously regarded as a tumor of misplaced rests of sebaceous-gland epithelium (Sutton and Sutton), as a basal-cell epithelioma with degeneration instead of differentiation of cells (Fink; Muehlon) or as a growth intermediary between epidermal cyst and basal-cell epithelioma (Côté). Turhan and Krainer expressed the opinion that calcifying epithelioma arises from hair-matrix cells. They believe that the basophilic cells are hair-matrix cells and that the formation of shadow cells represents a form of keratinization, an attempt at hair-shaft formation. In support of their theory, these authors point out that the basophilic cells resemble hair-matrix cells, that the small, round centers of keratinization observed in the epithelial formations of these tumors resemble cross-sections of hair shafts and that the melanin in some of these tumors is analogous to the melanin found in normal hair. Highman and Ogden have arrived at similar conclusions.

Lever and Griesemer regard the basophilic cells in calcifying epithelioma as primary epithelial germ cells with a tendency to differentiation into keratotic hair cells. The basophilic cells, thus, are assumed to have a function akin to that of hair-matrix cells, but, being less mature than hair-matrix cells, they produce not hair but irregular masses of immature hair cells (shadow cells). Accordingly, in a classification of primary epithelial germ tumors, calcifying epithelioma of Malherbe can be placed under those with differentiation toward hair structures (see Table 6, page 319).

Differential Diagnosis. Epidermal and sebaceous cysts may resemble calcifying epithelioma of Malherbe if their contents has un-

dergone partial calcification and if they have ruptured and, due to the resulting foreign-body giant-cell reaction, have undergone partial disintegration. They then share with calcifying epithelioma the presence of irregular islands of epithelial cells, of areas of calcification and of a foreign-body giant-cell reaction. However, basophilic cells and shadow cells are not found. It should be remembered that old lesions of calcifying epithelioma may show no more basophilic cells so that then the presence of shadow cells alone is the decisive factor in favor of calcifying epithelioma.

Differentiation of calcifying epithelioma from sebaceous cyst with secondary basal-cell epithelioma also rests largely on the presence of shadow cells since the areas of basophilic cells in calcifying epithelioma resemble basal-cell epithelioma; however, in calcifying epithelioma the epithelial structures never show palisading of the peripheral-cell layer and often there are areas in which one can observe the transformation of basophilic into shadow cells.

BASAL-CELL EPITHELIOMA

Basal-cell epithelioma may occur anywhere on the skin except on the palms and the soles. However, the face—particularly the periorbital region—is by far the most common site of location. The mucous membranes are never affected. Although basal-cell epithelioma occurs usually as a single lesion, multiple lesions are not infrequent. In occasional instances, the number of basal-cell epitheliomas present may exceed 100 (Nomland; Nisbet; Pautrier). Clinically, four types of basal-cell epithelioma occur: (1) nodulo-ulcerative basal-cell epithelioma, including rodent ulcer, (2) pigmented basal-cell epithelioma, (3) morphea-like or fibrosing basal-cell epithelioma and (4) superficial basal-cell epithelioma.

The nodulo-ulcerative type is the most common. It appears first as a small, waxy nodule which often shows on its surface a few telangiectatic vessels. The nodule slowly increases in size and undergoes central ulceration. A typical lesion then consists of a slowly progressing ulcer surrounded by a pearly, rolled border. This represents the rodent ulcer.

Pigmented basal-cell epithelioma differs from the nodulo-ulcerative type only by the dark pigmentation of the lesion.

Morphea-like or fibrosing basal-cell epithelioma manifests itself as an only slightly elevated, firm, yellowish plaque with ill-defined borders over which the skin remains intact for a long time before finally ulceration occurs.

Superficial basal-cell epithelioma consists of one or several erythematous, scaling, only slightly infiltrated patches surrounded by a fine,

threadlike, pearly border. The patches usually show small areas of superficial ulceration and crusting; in addition, their center may show smooth, atrophic scarring.

Basal-cell epitheliomas cannot be produced experimentally like squamous-cell carcinomas. However, they can develop following prolonged administration of inorganic arsenic (Anderson) (see page 155) and, in rare instances, in areas of radiodermatitis (Anderson and Anderson) (see page 122). Furthermore, basal-cell epitheliomas of the face occur much more frequently in areas with much sunshine, as in Australia and in the south of the United States, than in less sunny regions, such as England and the north of the United States.

Basal-cell epitheliomas do not metastasize, as a rule. It seems, however, that exceptions to this rule occur (Montgomery, 1928; Foot; Amersbach; Lattes and Kessler). Lattes and Kessler found a total of 20 cases of metastasizing basal-cell epitheliomas reported in the literature. Yet many authors doubt the occurrence of metastases in basal-cell epithelioma. Walther expressed the belief that cases reported as metastasizing basal-cell epithelioma represent wrong diagnoses.

Histogenesis. Several theories exist regarding the origin of basal-cell epithelioma. Krompecher, the original describer of basal-cell epithelioma, stated in 1903 that he regarded these tumors as carcinomas of the basal cells of the epidermis. He believed that those tumors which showed a tendency to gland formation imitated the embryonal gland formation of the basal cells. Krompecher's view is still adhered to by many (Montgomery, 1940; Teloh and Wheelock). However, Krainz believed that only those basal cells which develop into glandular cells gave rise to basal-cell carcinoma. Geschickter and Koehler shared this view. They suggested the designation appendage-cell carcinoma. Mallory and Haythorn held the opinion that basal-cell epitheliomas were carcinomas of hair-matrix cells.

Foot expressed the view that basal-cell epitheliomas were carcinomas which develop from distorted primordia of dermal adnexa rather than from ordinary epidermal basal cells. He stated that the tumors took origin from any or all three types of adnexal primordia, i.e., hair, sebaceous gland and sweat gland, and imitated their embryonal development.

The first author to express doubts that basal-cell epitheliomas were carcinomas was Adamson who, in 1914, stated that, in his opinion, basal-cell epitheliomas were nevoid tumors originating "from latent embryonic foci aroused from their dormant state at a later period of life." He believed that the latent embryonic foci usually were embryonic pilosebaceous follicles but occasionally were embryonic sweat ducts. Several authors have since reached similar conclusions. Re-

cently, Wallace and Halpert have suggested that basal-cell epitheliomas are benign tumors either of the hair matrix or of the hair anlage and have proposed the term trichoma for them.

It is the author's belief that basal-cell epitheliomas are not carcinomas, and are not derived from basal cells, but instead are nevroid tumors (hamartomas) derived from arrested, embryonal, primary epithelial germs. In other words, basal-cell epitheliomas originate from incompletely differentiated embryonal cells and not from de-differentiated, anaplastic cells. In accordance with the potentiality inherent in the primary epithelial germ to differentiate into sebaceous glands, apocrine glands and hair, differentiation in basal-cell epitheliomas can be either toward sebaceous gland, apocrine gland or hair structures. (See histogenesis and classification of epidermal tumors, page 317, and Table 6, page 319.)

Pinkus recently has suggested that basal-cell epitheliomas arise not from an embryonal rest, such as the primary epithelial germ, but from pluripotential cells which have formed during adult life and can, like the primary epithelial germ, differentiate in the direction of sebaceous glands, apocrine glands and hair. The fact that basal-cell epithelioma occasionally arises in areas of radiodermatitis and following the ingestion of arsenic is cited by Pinkus as evidence (although it could as well be assumed that these agents merely stimulate dormant primary epithelial germs to active growth).

Hueck has pointed out that, in basal-cell epitheliomas, the connective-tissue stroma always shows a close relationship to the tumor and proliferates with it, just as it does in benign fibro-epithelial tumors and in adenomas. On the other hand, in carcinomas the connective tissue usually is stretched, then tears until it finally disintegrates. He, therefore, regards basal-cell epithelioma not as a carcinoma but as a solid adenoma.

Histopathology. The characteristic cell of basal-cell epithelioma has a large, oval or elongated, deeply basophilic nucleus and little cytoplasm. The cytoplasm is often defined poorly, so that it may appear as if the nuclei were embedded in a symplasmic mass. The nuclei resemble those of the basal cells of the epidermis very closely, but the cells of basal-cell epithelioma differ from basal cells by not having intercellular bridges (see page 7).

In spite of the fact that it probably does not represent a true carcinoma, basal-cell epithelioma is an invasive tumor in most instances. Scattered islands of tumor cells are often found away from the main tumor deep in the dermis and even in the subcutaneous fat.

From a histologic point of view, basal-cell epitheliomas can be divided into two main groups—undifferentiated and differentiated, the

latter showing differentiation toward primary epithelial germ structures—i.e., toward sebaceous glands, apocrine glands or hair. A sharp dividing line between the two groups cannot be drawn, because many undifferentiated basal-cell epitheliomas show differentiation in some areas, and most differentiated basal-cell epitheliomas show areas lacking differentiation. Correlating the clinical with the histologic classification, it can be stated that the nodulo-ulcerative type of basal-cell epithelioma may be differentiated or undifferentiated, whereas pigmented basal-cell epithelioma, fibrosing basal-cell epithelioma and superficial basal-cell epithelioma usually are undifferentiated. If the nodulo-ulcerative basal-cell epithelioma shows no differentiation, it is called solid basal-cell epithelioma; if it shows differentiation, it may be either a cystic, an adenoid or a keratotic basal-cell epithelioma.

I. UNDIFFERENTIATED BASAL-CELL EPITHELIOMAS. The group of undifferentiated basal-cell epitheliomas includes the solid basal-cell epithelioma, the pigmented basal-cell epithelioma, the morphea-like or fibrosing basal-cell epithelioma and the superficial basal-cell epithelioma.

A. SOLID BASAL-CELL EPITHELIOMA (primordial type of basal-cell epithelioma, Foot). In this form, variously sized and shaped masses of tumor cells are embedded in the dermis (Fig. 192). Some of the masses originate from the surface epidermis but others show no connections with it, even on serial sections. In occasional instances, one sees a mass of tumor cells originate from the epidermis of a hair follicle. In the masses of tumor cells, the nuclei of the peripheral layer of cells often show palisade arrangement, whereas the nuclei of the cells inside lie in haphazard fashion.

A mild or moderately severe inflammatory reaction may be present in the dermis, particularly in the more rapidly growing tumors, but it may be entirely lacking. The connective tissue frequently proliferates with the tumor and is arranged in parallel bundles around the tumor masses so that a definite mutual relationship seems to exist between the parenchyma of the tumor and its stroma (Hueck; Pinkus). The connective tissue nearest to the tumor masses often undergoes mucinous degeneration. Since mucin shrinks during fixation, the stroma frequently retracts from the tumor islands so that in prepared sections the tumor islands seem to lie free in cavities (Fig. 201). Although this retraction represents merely an artefact caused by shrinkage during fixation, it is quite typical of basal-cell epithelioma and aids in differentiating it from other tumors such as squamous-cell carcinoma. The epidermis overlying basal-cell epithelioma often is atrophic. Ulceration is common ("rodent ulcer").

Some basal-cell epitheliomas with little or no structural differentiation toward the cutaneous appendages show evidence, nevertheless, of cellular differentiation by presenting two types of cells. One type of cell has small, elongated, deeply basophilic nuclei; the other has



FIG. 192. Solid basal-cell epithelioma (undifferentiated or primordial basal-cell epithelioma). There are variously sized and shaped masses of "basal cells." The peripheral cell layer in the masses shows palisade arrangement of nuclei. ($\times 200$)

large, round, pale-staining, vesicular nuclei (Fig. 193). The former may be regarded as cells differentiating toward either myo-epithelial cells of apocrine glands or hair-matrix cells, while the latter probably are cells differentiating toward secretory cells of either sebaceous or apocrine glands.

B. PIGMENTED BASAL-CELL EPITHELIOMA. Although the presence of melanin can be demonstrated by silver stains in many basal-cell epitheliomas (Becker), large amounts are encountered only rarely. The

presence of melanin in basal-cell epitheliomas can be explained by the fact that melanin-producing melanocytes are present not only in the surface epidermis but also in the primary epithelial germ. (As the primary epithelial germ matures into the hair, these melanocytes arrange themselves among the hair-matrix cells overlying the hair papilla and form the melanin of the hair. (See Fig. 9.)

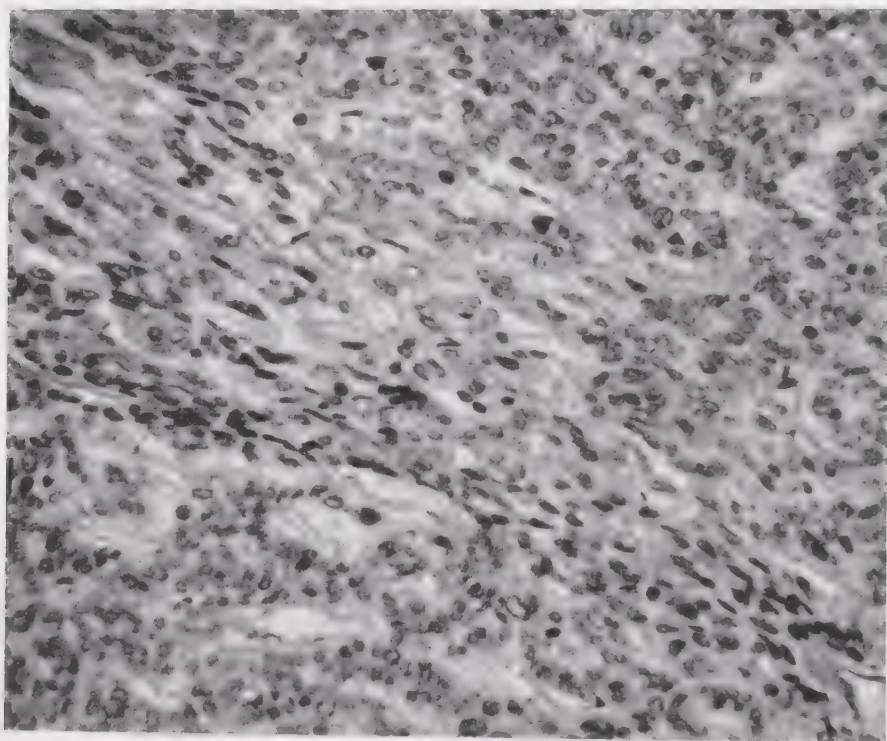


FIG. 193. Basal-cell epithelioma with differentiation into two types of cells. One type of cell has large, oval, pale nuclei; the other type has small, elongated, dark nuclei. ($\times 400$)

Basal-cell epitheliomas with large amounts of pigment contain, interspersed between the tumor cells, numerous melanin-laden melanocytes (Bloch). The connective tissue of these tumors contains numerous melanophores (Eller and Anderson; Becker; Foot).

C. MORPHEA-LIKE OR FIBROSING BASAL-CELL EPITHELIOMA. In this variant, connective-tissue proliferation is much greater than in the other types of basal-cell epithelioma. Embedded in a dense, fibrous stroma, one observes innumerable groups of closely packed tumor cells arranged in elongated strands (Fig. 194) (Caro and Howell). Most of the strands are small, but others are larger and show branching. The groups of tumor cells often extend deeply into the dermis.

D. SUPERFICIAL BASAL-CELL EPITHELIOMA. This type of basal-cell epithelioma originates from the epidermis in multiple foci (Fig. 195).

The peripheral-cell layer of the budlike proliferations usually shows palisade arrangement. There is little penetration into the dermis. It may be pointed out that the epidermal buds often show great resemblance to the primary epithelial germ buds as seen in the em-

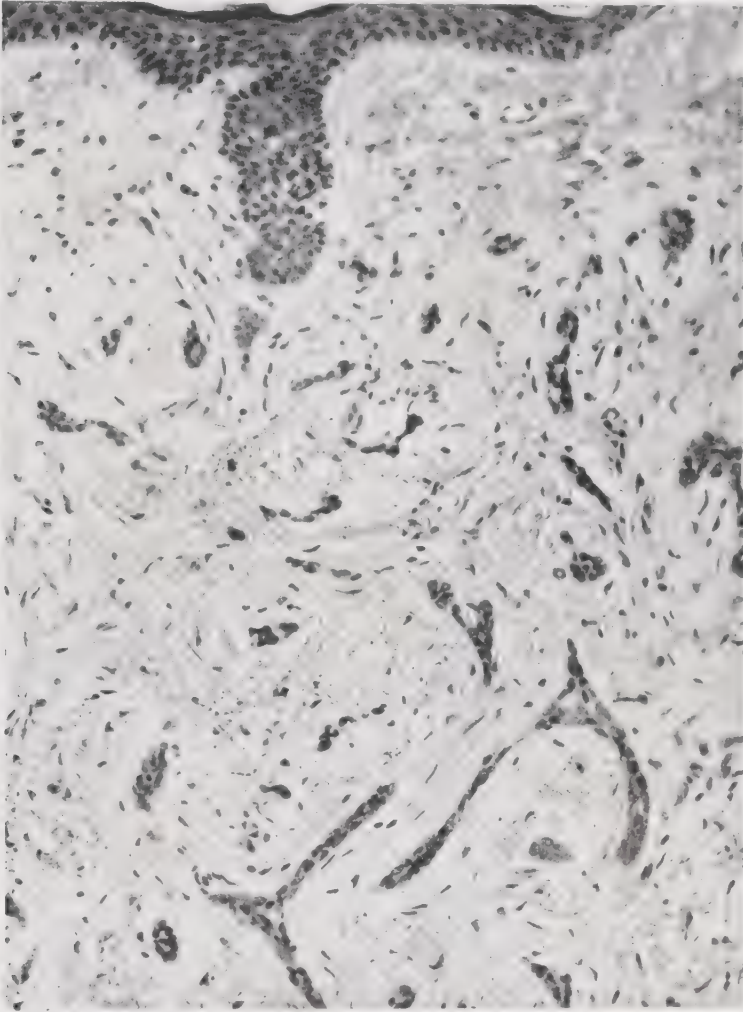


FIG. 194. Morphea-like or fibrosing basal-cell epithelioma. Innumerable small groups of closely packed tumor cells, many of them arranged in elongated strands, are embedded in a dense, fibrous stroma. ($\times 100$)

bryonal skin (see Figure 1). The overlying epidermis usually shows atrophy but may show acanthosis and papillomatosis. A mild to moderate amount of inflammatory infiltrate composed of lymphocytes and plasma cells is present in the upper dermis (Wise; Montgomery, 1929).

Some superficial basal-cell epitheliomas, after having persisted as such for various lengths of time, become true invasive basal-cell epi-

theliomas. Since this change may at first be limited to a few areas, representative sections throughout the entire tissue block should be examined.

A rare type of superficial basal-cell epithelioma is the intra-epidermal type. In this type, the epidermis shows acanthosis. Embedded in the broadened epidermis one finds multiple, sharply demarcated foci of basal-cell epithelioma. The tumor cells stand out clearly from the surrounding epidermis by their strongly basophilic staining (Montgomery, 1929; Sims and Parker).

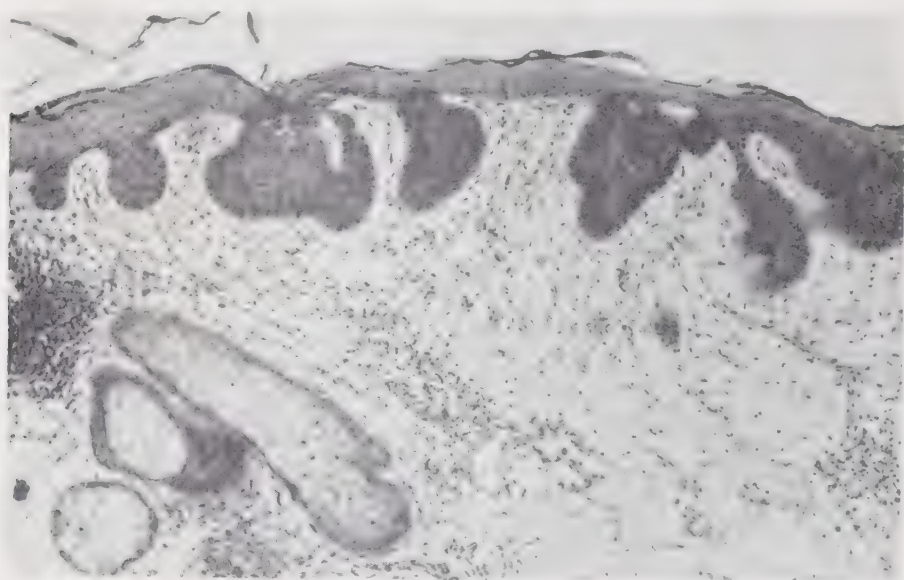


FIG. 195. **Superficial basal-cell epithelioma.** The tumor shows multiple points of origin from the epidermis. Note the similarity between the tumor buds in this illustration and the primary epithelial germ buds in the embryonal skin shown in Figure 1. ($\times 100$)

2. **DIFFERENTIATED BASAL-CELL EPITHELIOMAS.** Differentiation in basal-cell epitheliomas may proceed in three directions, toward sebaceous glands, apocrine glands or hair (Foot; Lever). Those with differentiation toward sebaceous glands are called cystic, those with differentiation toward apocrine glands are called adenoid, and those with differentiation toward hair are called keratotic basal-cell epitheliomas. In most differentiated basal-cell epitheliomas, differentiation is directed toward more than one of the three structures. For example, areas of keratinization may be found in a tumor which also shows glandular structures.

A. **CYSTIC BASAL-CELL EPITHELIOMA.** In this type, cystic spaces are present in the center of the tumor masses. The cysts may form in three ways: by degeneration of stroma that has become enclosed into the tumor; by degeneration of the center of the tumor masses; and

by differentiation of the cells in the center of the tumor masses toward sebaceous cells and subsequent disintegration analogous to the disintegration of sebaceous cells in the process of forming their secretion. In the latter type of cyst formation, some of the tumor cells in the vicinity of the cyst are apt to be vacuolated (Foot) or even foamy (Piérard and Dupont) (Fig. 196).

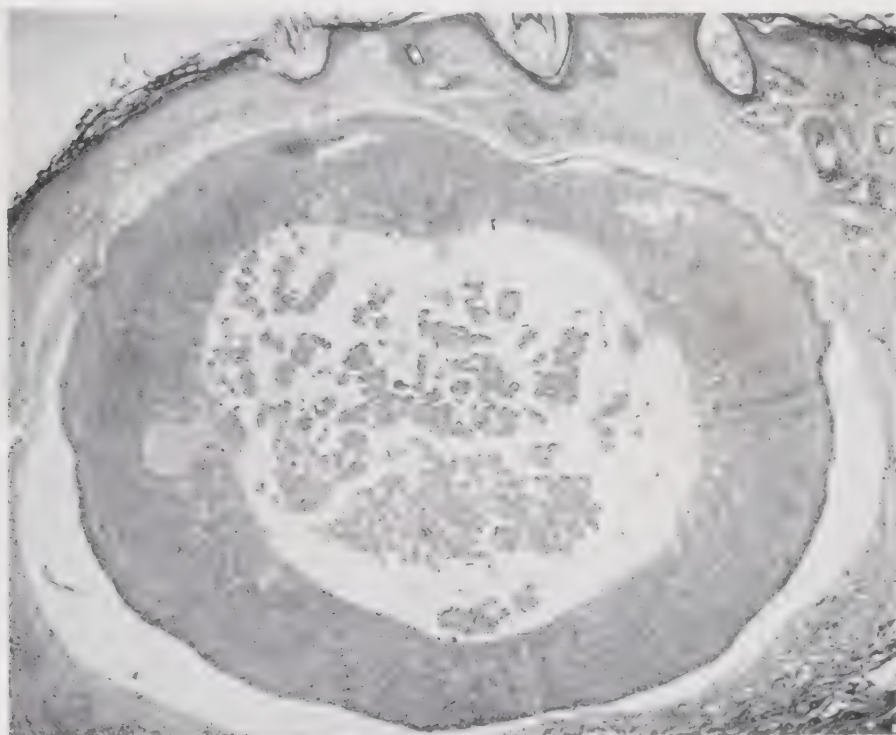


FIG. 196. Cystic basal-cell epithelioma. The cyst has formed by disintegration of cells with sebaceous differentiation. ($\times 50$)

B. ADENOID BASAL-CELL EPITHELIOMA. This type of tumor shows formations suggesting tubular, glandlike structures. The cells are arranged in intertwining strands and radially around islands of connective tissue, resulting in a "lacelike" patterning of the tumor (Fig. 197). In some tumors, one may find lumina surrounded by cells which have the appearance of glandular cells. The lumina may be filled by a colloidlike substance or by granular material, but definite evidence of secretory activity of the glandular cells is missing (Fig. 198).

C. KERATOTIC BASAL-CELL EPITHELIOMA (pillar type, Foot). In this type, cells with elongated nuclei and slightly eosinophilic cytoplasm are seen traversing the tumor as short bands or are arranged in concentric layers around parakeratotic or keratotic centers. As pointed out by Krompecher, who first described this type of basal-cell epi-

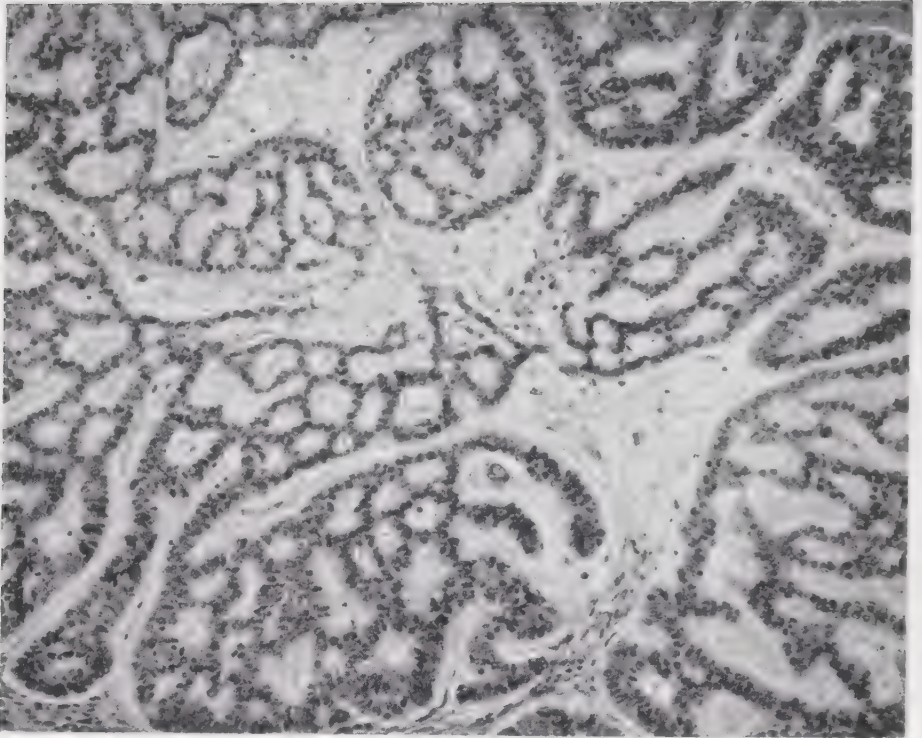


FIG. 197. Adenoid basal-cell epithelioma. The strands of epithelial cells show a "lacelike" pattern. The stroma shows mucoid degeneration. ($\times 200$)

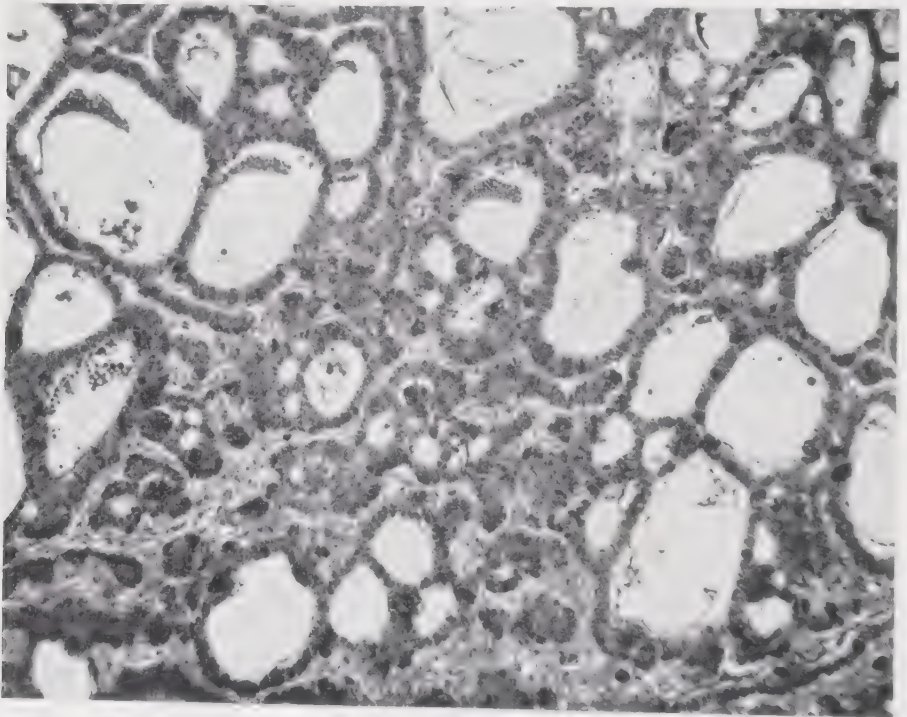


FIG. 198. Adenoid basal-cell epithelioma. The tumor contains lumina surrounded by cells that have the appearance of glandular cells. ($\times 200$)

thelioma, the elongated cells cornify abruptly so that the parakeratotic or keratotic centers are sharply demarcated against the surrounding cells (Fig. 199).

The cells surrounding the parakeratotic and keratotic centers have the appearance of hair-matrix cells. Just as, normally, the hair cells develop from hair-matrix cells by abrupt keratinization, so the keratotic or parakeratotic centers in keratotic basal-cell epithelioma develop from hair-matrix cells and represent attempts at hair-shaft formation (Foot). The keratinization in keratotic basal-cell epithelioma thus is one of hair-matrix cells, which are cells without prickles, and not one of squamous cells.

Some keratotic basal-cell epitheliomas possess large centers of keratinization, so-called horn cysts (Fig. 200). They are like those observed in tricho-epithelioma (page 363). These horn cysts must not be confused with the horn pearls that occur in squamous-cell carcinoma (see below, under differential diagnosis).

"BASAL-SQUAMOUS-CELL EPITHELIOMA." Several authors (Darier and Ferrand; Montgomery, 1928; Juon) have described basal-cell epitheliomas with features of squamous-cell carcinoma. According to Montgomery, they represent "metamorphosis of basal-cell to squamous-cell epitheliomas." He stated that from 15 to 20 per cent of all basal-cell epitheliomas present such changes.

Two types of basal-squamous-cell epithelioma are recognized by the authors named above: a mixed and an intermediary type. The mixed type is described as showing partial horn pearl formation with a parakeratotic rather than a horny center. The intermediary type is described as showing two kinds of cells, those with small, elongated, deeply basophilic nuclei, regarded as basal cells, and those with large, round, pale-staining nuclei, regarded as intermediary in character between basal and squamous cells.

The existence of basal-squamous-cell epithelioma is not generally accepted (Lever; Welton, Elliott and Kimmelstiel; Lennox and Wells). It is likely that the mixed type of basal-squamous-cell epithelioma represents a keratotic basal-cell epithelioma (Fig. 199) and the intermediary type a solid basal-cell epithelioma in which the cells with large, round, pale-staining nuclei show differentiation toward secretory cells of either sebaceous or apocrine glands (Fig. 193) (see page 373).

"MIXED CARCINOMA." These tumors show a squamous-cell carcinoma contiguous to a basal-cell epithelioma (Fig. 201). The author believes that, in such instances, the squamous-cell carcinoma develops secondary to the basal-cell epithelioma. Like other chronic ulcerative

lesions (for instance, lupus vulgaris, gumma and burns), basal-cell epithelioma may stimulate the development of a squamous-cell carcinoma. Before making a diagnosis of "mixed carcinoma," one must rule out the possibility of pseudo-epitheliomatous hyperplasia occurring in a basal-cell epithelioma (see page 334).

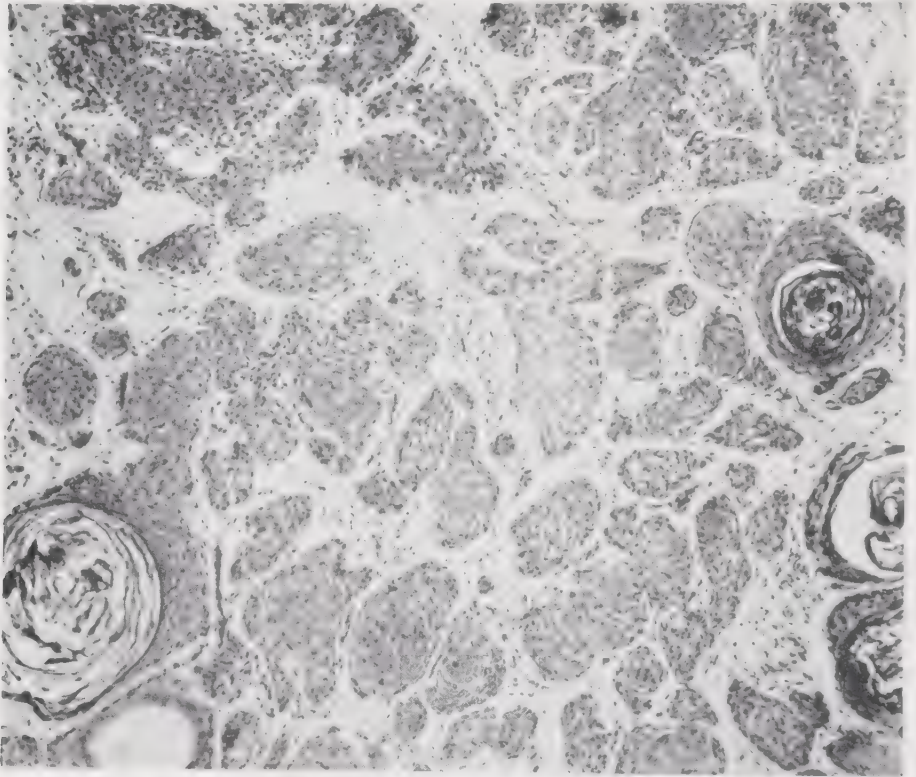


FIG. 199. Keratotic basal-cell epithelioma (pilar type of basal-cell epithelioma). The cell masses in this tumor are composed largely of elongated cells lying in concentric arrangement. Several of the cell masses contain a horn cyst in their center. The elongated cells contain no prickles; they represent hair-matrix cells. Note the abrupt and complete keratinization in the horn cysts. ($\times 100$)

Differential Diagnosis. Differentiation of basal-cell epithelioma from squamous-cell carcinoma may be difficult at times—so difficult that many authors have decided that intermediary forms ("basal-squamous-cell epithelioma") occur. As a rule, however, differentiation is fairly easy. One of the best points of differentiation is that the cells of basal-cell epithelioma stain deeply basophilic, whereas most cells of squamous-cell carcinoma, at least in Grades I and II, have an eosinophilic tint due to partial or complete keratinization. In squamous-cell carcinoma, Grades III and IV, the cells, because of

the absence of keratinization, may appear basophilic. However, they differ from those of basal-cell epithelioma by showing much more atypicality and more mitotic figures. It is important to remember that keratinization is not a prerogative of squamous-cell carcinoma

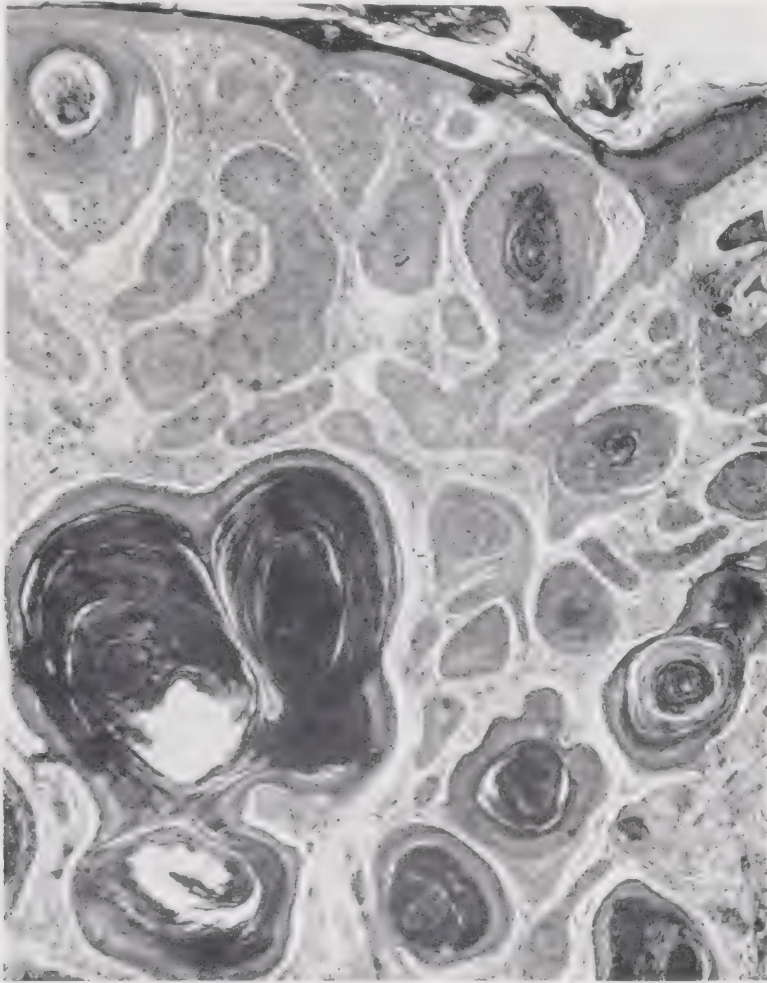


FIG. 200. Keratotic basal-cell epithelioma. This tumor contains unusually large horn cysts. ($\times 50$)

but occurs also in basal-cell epitheliomas with differentiation toward hair structures. (See "Keratotic Basal-Cell Epithelioma," page 377.) Keratinization in basal-cell epitheliomas may be partial ("parakeratotic centers") or complete ("horn cysts"). The keratinization differs from that seen in the horn pearls of squamous-cell carcinomas by occurring abruptly without the interposition of gradually keratinizing squamous cells. The fairly common presence in basal-cell epithelioma of areas of retraction of the tumor cell masses from the sur-

rounding connective tissue (see page 372) also aids in differentiating it from squamous-cell carcinoma, since such areas of retraction are not found in the latter.

The differential diagnosis between basal-cell epithelioma and tricho-epithelioma already has been discussed (see page 364).

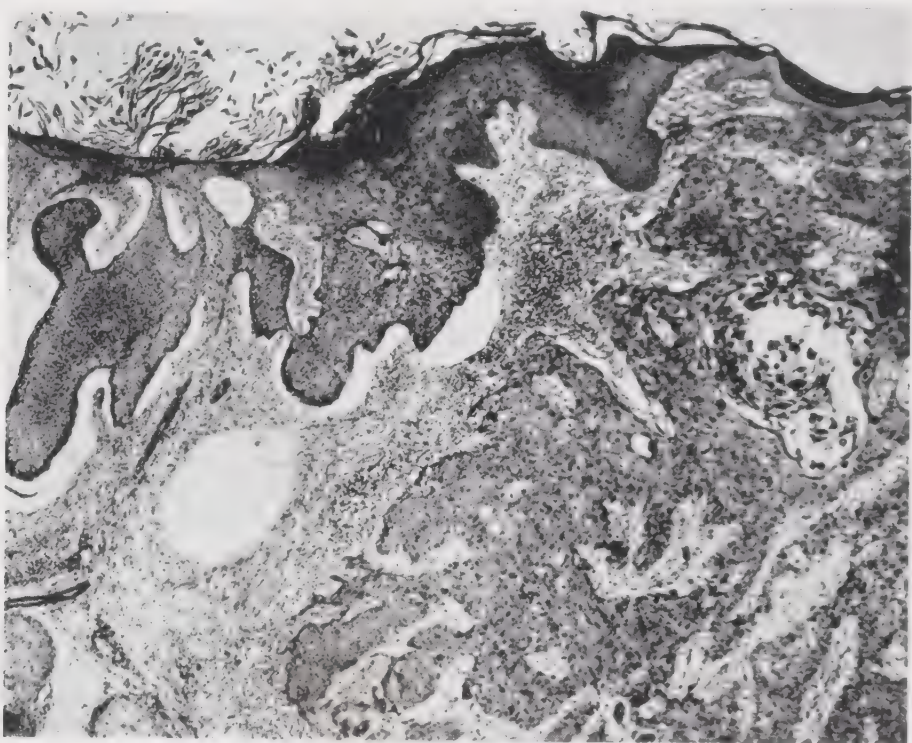


FIG. 201. "Mixed carcinoma." A basal-cell epithelioma (*left*) and a squamous-cell carcinoma (*right*) lie side by side. ($\times 50$)

BASAL-CELL PAPILLOMA (VERRUCA SENILIS, KERATOSIS SEBORRHEICA)

Basal-cell papillomas develop, often in large numbers, on the trunk, the face and the arms in persons past middle life. They are sharply circumscribed, slightly raised, verrucous, more or less pigmented lesions which often look as if "stuck on" the surface of the skin. The verrucous covering of the lesions tends to have a soft, greasy consistency. Although most lesions measure only a few millimeters in diameter, an occasional lesion may reach a size of several centimeters.

Histopathology. This tumor represents a squamous-cell papilloma in which there are areas of proliferation of cells of the same type as seen in basal-cell papilloma.

Basal-cell papillomas occur in two types: a keratotic and an ade

noid type (Hookey). The former type is more common than the latter. Frequently, however, both types occur in the same lesion.

The keratotic type of basal-cell papilloma shows considerable hyperkeratosis, acanthosis and papillomatosis. The acanthosis is due entirely to upward growth of epithelial cells. Thus, the lower base of the tumor lies above a straight line that may be drawn from the normal epidermis at one end of the tumor to the normal epidermis at the other end, and the lesion appears as though tacked on the sur-

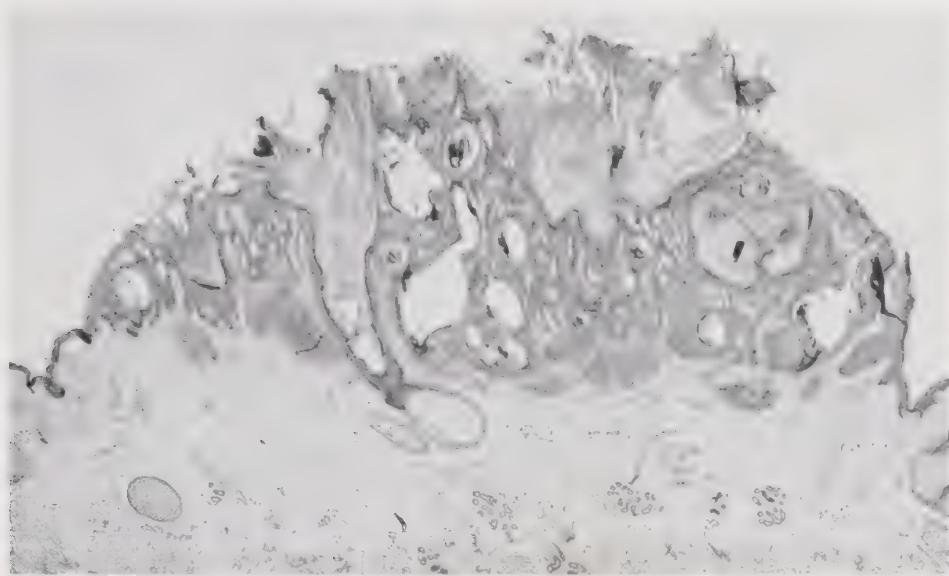


FIG. 202. Basal-cell papilloma, keratotic type. Low magnification. The superficial location of the tumor is apparent. The lesion appears as if tacked on the epidermis. ($\times 25$)

face of the skin (Fig. 202). The acanthosis is due in part to proliferation of squamous cells, but, to a significant degree, due also to proliferation of cells of the same type as seen in basal-cell epithelioma. The tumor may be solid but usually consists of thick, interwoven tracts of epithelial cells surrounding islands of connective tissue. The horny layer invaginates, in places, deep into the lesion. Because of the tortuosity of these invaginations, cystic inclusions of horny material result (Fig. 203). They are surrounded by a shell of squamous cells. Melanin is present in most of these tumors, usually in small amounts but occasionally in considerable quantities (Becker). It is located in the areas of "basal-cell" proliferation. Melanocytes ("clear cells") are prominent in the pigmented portions.

The adenoid type of basal-cell papilloma shows, originating from the epidermis, numerous thin tracts composed of a double row of cells. These cells resemble those of basal-cell epitheliomas. The tracts



FIG. 203. Basal-cell papilloma, keratotic type. High magnification. Thick, interwoven tracts of "basal cells" compose the tumor. Interspersed are cystic inclusions of horny material caused by invaginations of the horny layer. ($\times 100$)

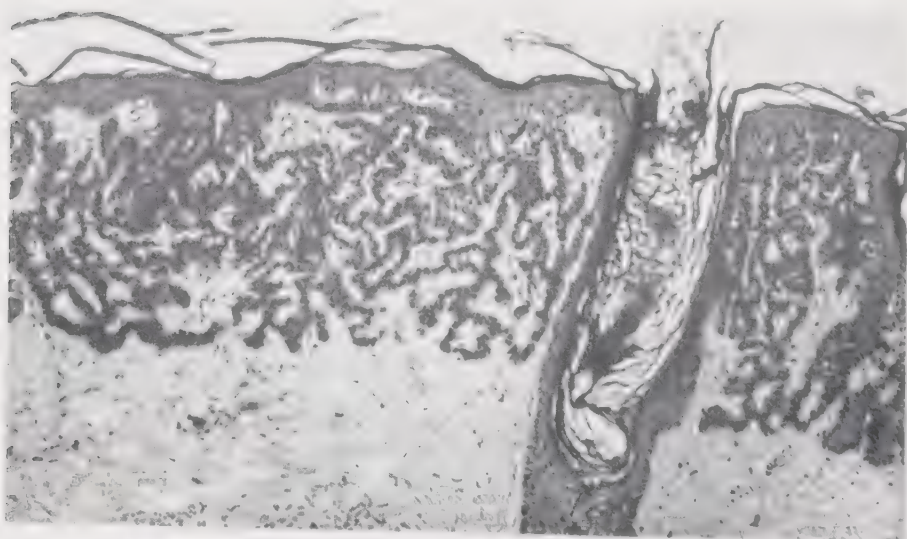


FIG. 204. Basal-cell papilloma, adenoid type. Thin, interwoven tracts composed of a double row of "basal cells" compose the tumor. No cystic inclusions of horny material are present. ($\times 100$)

branch and interweave (Fig. 204). Considerable amounts of melanin usually are present in the tracts. Cystic inclusions of horny material are absent. The demarcation at the lower border is sharp, just as in the keratotic type of basal-cell papilloma.

Although basal-cell papilloma shows no tendency to invasion of the dermis, it may be regarded as related to basal-cell epithelioma, because a large proportion of the cells are of the same type as found in basal-cell epithelioma. However, actual change of basal-cell papilloma into a frank basal-cell epithelioma with deep invasion and ulceration is rare (Eller and Ryan; Pinkus).

(For differential diagnosis from *nexus verrucosus*, see page 322, and from *keratosis senilis*, see page 328.)

DERMATOSIS PAPULOSA NIGRA

This condition is frequent among Negroes, especially females. The lesions are located on the face, especially in the malar regions, and consist of minute, soft, rounded, usually hyperpigmented papules.

Histopathology. The histologic changes are the same as in basal-cell papilloma. Melanin pigmentation of the basal layer is pronounced (Michael and Seale).

CARCINOMA OF SEBACEOUS GLANDS

Carcinomas of sebaceous glands have been described occasionally in the literature. Some authors are more inclined to make this diagnosis than others. Warren and Warvi, for instance, reported 28 personally observed cases, while most other authors have reported only single instances (Beach and Severance).

Carcinomas of sebaceous glands occur most frequently on the eyelids, originating from meibomian glands, which are modified sebaceous glands (Hagedoorn); they may, however, occur anywhere on the skin (Beach and Severance). No characteristic clinical picture is associated with sebaceous carcinoma. As a rule, the lesion consists of an ulcerated nodule. Metastasis is relatively frequent.

Histopathology. One observes definite lobular formations (Fig. 205). Although many cells are undifferentiated, distinct sebaceous cells are present. Mitotic figures are numerous. Lipid material can be demonstrated, not only in the sebaceous cells but also as fine globules in many other cells of the tumor. Beach and Severance state that the undifferentiated cells of sebaceous carcinoma differ from those of basal-cell epithelioma by showing greater variation in size and shape and by having a more acidophilic cytoplasm and a lighter staining nucleus.

It seems that many cases reported as sebaceous carcinoma may be regarded as sebaceous adenoma (see page 347) or as sebaceous epithelioma, which is a basal-cell epithelioma with considerable differentiation of the cells toward sebaceous gland cells (page 353). For in-

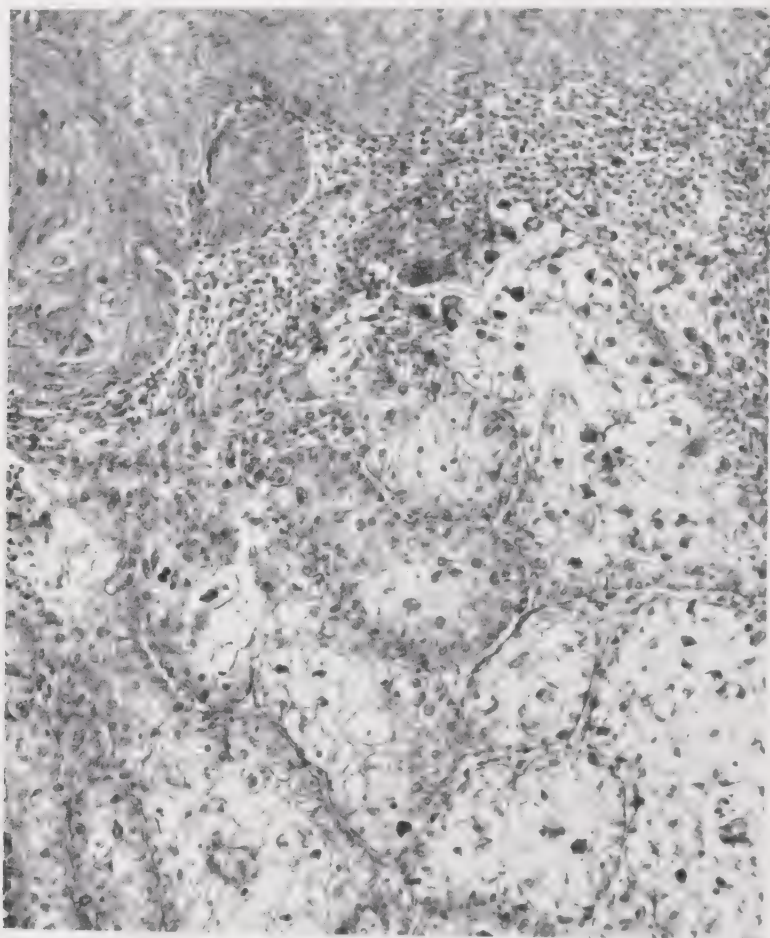


FIG. 205. Carcinoma of sebaceous glands. Closely packed lobular formations are present in the dermis. They are composed of sebaceous and undifferentiated cells. Some of the latter are atypical. ($\times 200$)

stance, the five cases of sebaceous carcinoma reported by Savatard as arising in cases of nevus sebaceus are best classified as instances of sebaceous epithelioma.

CARCINOMA OF ECCRINE SWEAT GLANDS

Carcinomas of the eccrine sweat glands are rare, but their existence seems to be established definitely. They do not possess a characteristic appearance, either clinically or histologically.

Histopathology. It is difficult to recognize carcinoma of eccrine sweat glands and to differentiate it from other cutaneous tumors, especially adenoid basal-cell epithelioma.

Loos has suggested a classification of carcinomas of sweat glands by dividing them into alveolar, tubular, cystic-papillary and solid forms. He pointed out that combinations of these forms were frequent. He recognized the occasional occurrence of metaplasia of glandular cells into squamous and horn cells.

ADENO-ACANTHOMA OF SWEAT GLANDS

Carcinomas of sweat glands with glandular as well as epidermal elements have recently been reported under the designation adeno-acanthoma of sweat glands (Lever).

Clinically, these tumors resemble squamous-cell carcinoma. They show shallow central ulceration and may have a verrucous surface. Their site of predilection is the face, especially the ears.

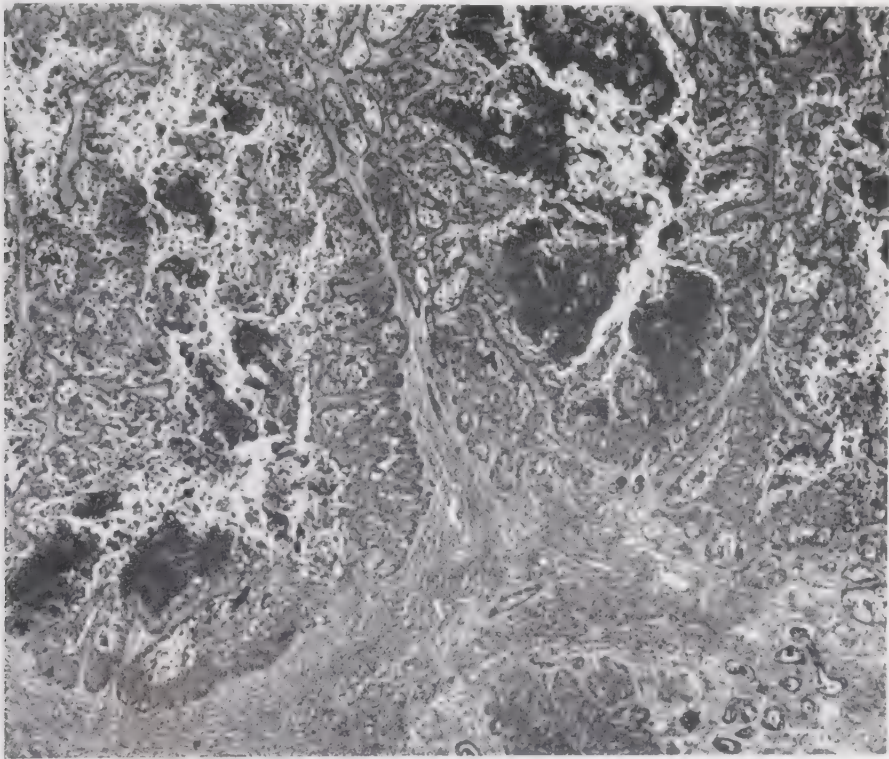


FIG. 206. Adeno-acanthoma of sweat glands. Low magnification. The tumor contains large alveolar spaces into which papillary projections protrude. The alveolar spaces are filled with desquamated cells, most of which are either partially or fully keratinized. In the granulation tissue beneath the alveolar formations, an island of tumor tissue and several atypical sweat glands or ducts are present. ($\times 50$)

Histopathology. Adeno-acanthomas show tubular and alveolar lumina lined with one or several layers of epithelium (Fig. 206). In areas where the lumina are lined with a single layer of epithelium, the epithelial cells have the appearance of glandular cells, but in areas with several layers of epithelium, squamous and partially keratinized cells usually form the inner layers. The lumina are filled with

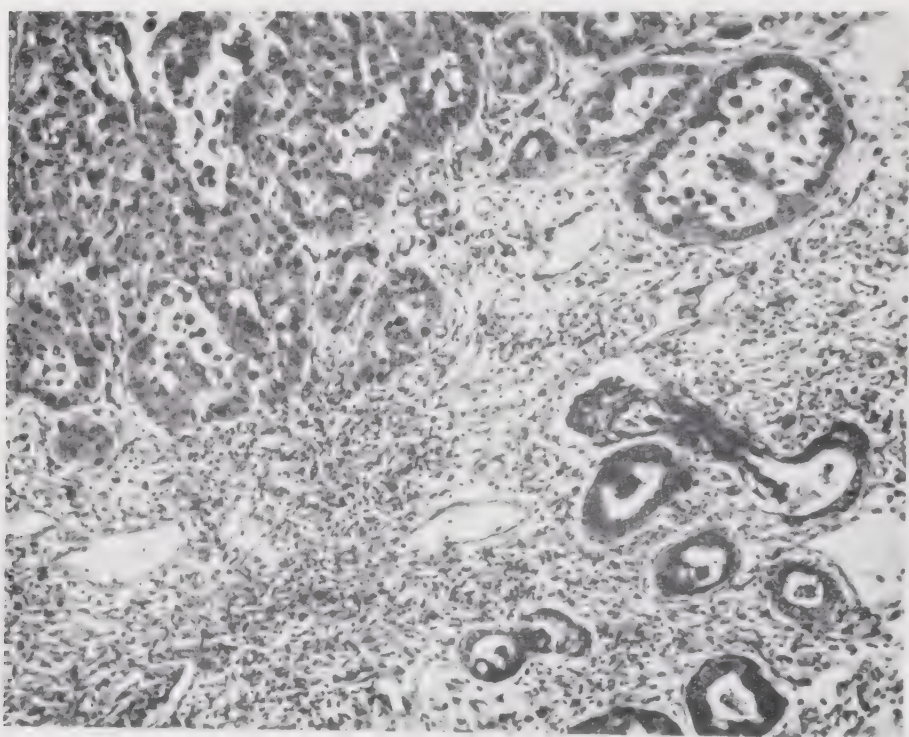


FIG. 207. Adeno-acanthoma of sweat glands. High magnification of the atypical sweat glands or ducts seen in Figure 206. Papillary tufts protrude into their lumina. These sweat glands approach in appearance the glandular structures belonging to the tumor. ($\times 200$)

desquamated cells, many of which are partially or completely keratinized. In addition, there are solid areas which have the appearance of squamous-cell carcinoma. Atypical eccrine sweat glands and sweat ducts are present within or at the periphery of these tumors (Fig. 207).

Histogenesis. The author originally regarded these tumors as sweat-gland carcinomas composed of glandular and epidermal elements and explained the presence of these two structures by the fact that sweat ducts are composed of squamous cells in their epidermal portion, and of glandular cells in the dermis. It is possible, however, that these tumors are squamous-cell carcinomas of alveolar growth in which there is considerable individual cell keratinization, resulting in acantholysis in the center of the alveolar formations.

Borelli regards these tumors as dyskeratotic squamous-cell carcinomas "which arise from the hair follicle and tend to imitate the structure of glands which develop embryologically together with the follicle."

CARCINOMA OF APOCRINE GLANDS

Extramammary Paget's disease represents a carcinoma of apocrine glands (see page 339). No other form of carcinoma of apocrine glands has so far been established.

METASTATIC CARCINOMA OF THE SKIN

Cutaneous metastasis of carcinoma is rare, with the exception of carcinoma of the breast. Next to carcinoma of the breast, metastases

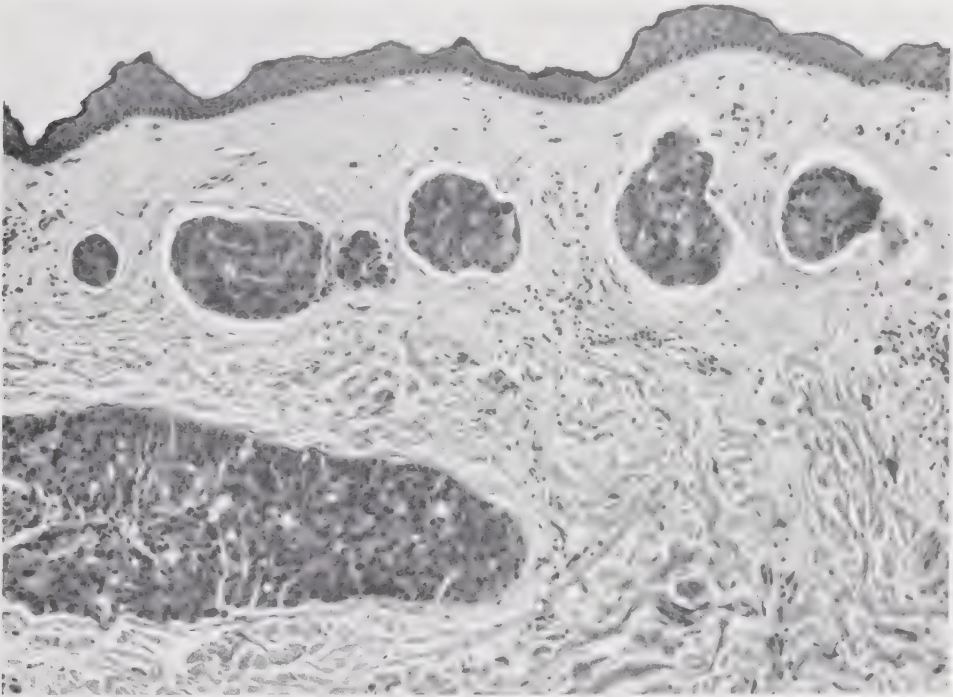


FIG. 208. Metastatic carcinoma of the skin from carcinoma of the breast. Inflammatory carcinoma. The dermal lymphatics are filled with clusters of tumor cells. ($\times 100$)

to the skin are observed most frequently in carcinoma of the stomach, the uterus, the lungs, the large intestines and the kidneys, in that order (Gates). In occasional instances, cancer of the prostate (Ronchese), of the testes (Murrell and Pepple), of the bladder (McDonald, Heckel and Kretschmer), of the pancreas (Edelstein) and of the ovary (Urbach, Waldow and Stamm) may lead to cutaneous metastases.

Dissemination may take place through the lymphatics or through the blood stream. In carcinoma of the breast, cutaneous metastases

usually are caused by way of the lymphatics. In other carcinomas, cutaneous metastases, as a rule, are caused by dissemination through the blood stream, although occasionally dissemination takes place through lymphatics secondary to local lymph node involvement (Gates).

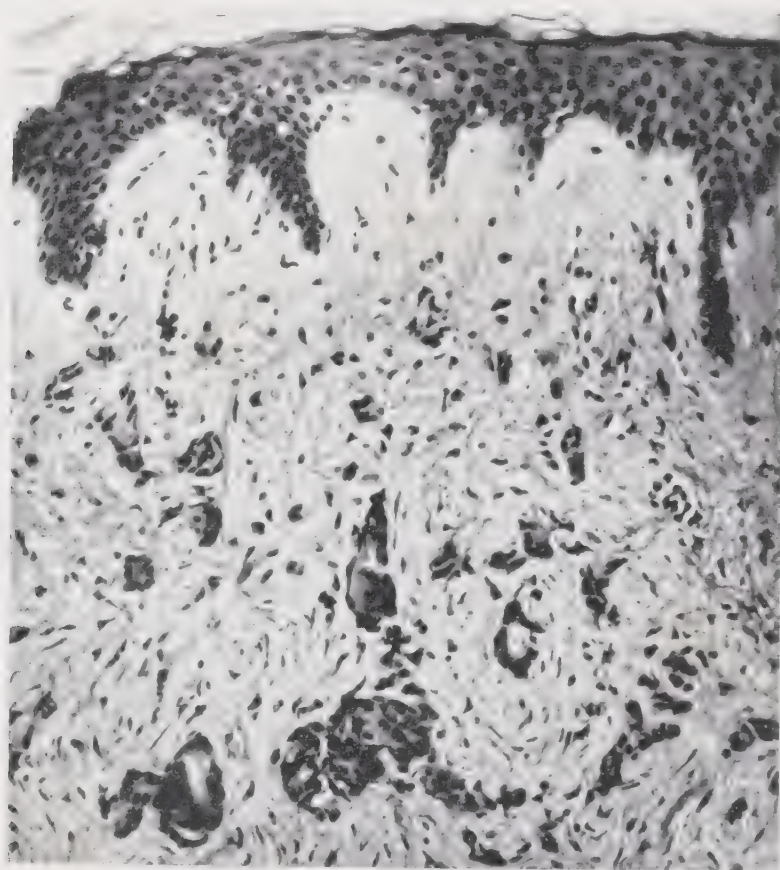


FIG. 209. Metastatic carcinoma of the skin from carcinoma of the breast. Cancer en cuirasse, nodular lesion. There is considerable fibrosis of the dermis with small, scattered islands of tumor cells. Some of the islands show a suggestive glandular arrangement of the tumor cells. ($\times 200$)

CUTANEOUS METASTASIS FROM CARCINOMA OF THE BREAST

Three types of cutaneous metastases may occur in carcinoma of the breast: inflammatory carcinoma, telangiectatic carcinoma, and cancer en cuirasse. Two or all three of these types may be present in the same patient. If dissemination of metastases through the lymphatics proceeds rapidly, inflammatory carcinoma results in most instances, and telangiectatic carcinoma in rare instances. If dissemination proceeds slowly, cancer en cuirasse eventuates (Taylor and Meltzer).

In inflammatory carcinoma, the skin of the affected breast and the adjoining areas present erythema and diffuse edema simulating erysipelas. In telangiectatic carcinoma, the skin contains numerous purplish papules and hemorrhagic pseudovesicles resembling hemolympangioma. In cancer en cuirasse, the skin of the breast affected by the carcinoma, and often also the surrounding skin, shows dif-



FIG. 210. Metastatic carcinoma of the skin from carcinoma of the breast. Cancer en cuirasse, indurated area. Only few tumor cells are present. They lie embedded between collagen bundles in single-row lines. Because of their small number and size, they may be overlooked easily. ($\times 400$)

fuse, brawny induration interspersed with nodules and punched-out ulcerations.

Histopathology. In inflammatory carcinoma, histologic examination of the skin reveals extensive invasion of the dermal lymphatics—especially of the subepidermal lymphatics—by groups and cords of tumor cells (Fig. 208) (Taylor and Meltzer). The tumor cells are similar to those of the primary growth, atypical in character, with large, rounded, deeply staining nuclei and a moderate amount of cytoplasm. Occasional mitoses are seen in these cells. There is marked capillary congestion (which is the reason for the inflammatory appearance clinically). In addition, one observes edema and a slight perivascular lymphocytic infiltrate in the dermis but no fibrosis (Pfahler and Case).

In telangiectatic carcinoma, the dilated lymphatics contain, in addition to groups of tumor cells, varying amounts of erythrocytes (Freeman and Lynch; Leavell and Tillotson). The frequent location of these lymphatics immediately beneath the epidermis causes the clinical resemblance of the lesions to vesicles.

In cancer en cuirasse, the nodular areas usually contain large and small groups as well as sheets of tumor cells lying outside of lymphatics in the dermis and surrounded by fibrosis (Fig. 209). However, the indurated areas often contain only few tumor cells which, therefore, may be easily overlooked. The tumor cells are small, angular and deeply basophilic and lie as single cells, in single-row lines or small groups between thickened collagen bundles. The arrangement in single-row lines, "like Indians in a file," is of particular diagnostic importance (Fig. 210).

CUTANEOUS METASTASIS FROM CARCINOMAS OTHER THAN BREAST CARCINOMA

The cutaneous metastases caused by carcinomas of organs other than the breast occur clinically as circumscribed nodules or tumors. The nodules are usually discrete and moderately firm. Their number may vary from one to several hundred.

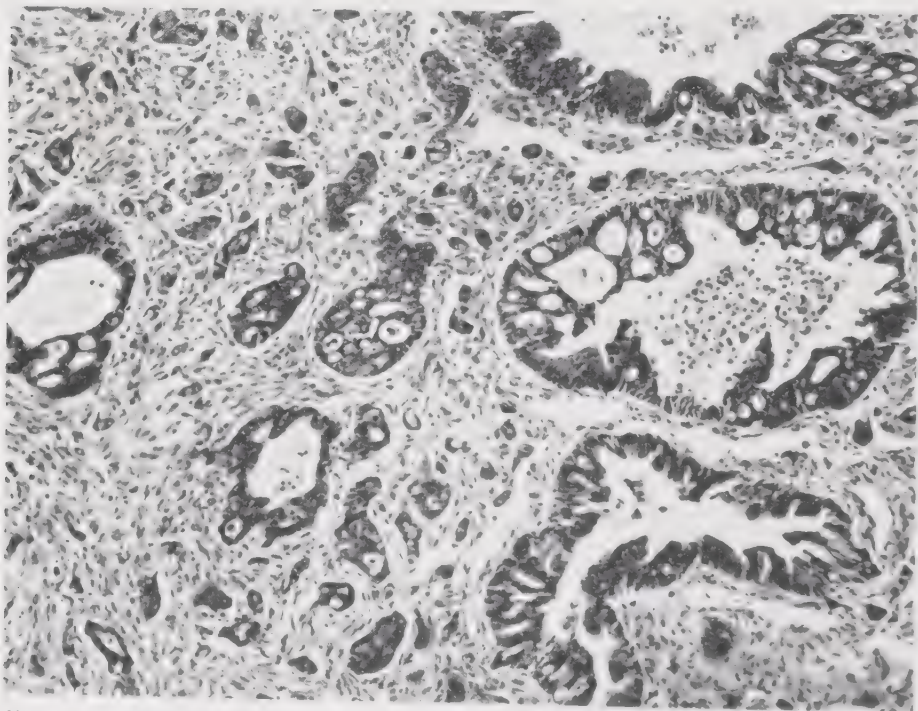


Fig. 211. Metastatic adenocarcinoma of the skin. Numerous glandular lumina are present. ($\times 100$)

Histopathology. Large and small groups of tumor cells are present throughout the dermis. As a rule, no tumor cells are found within capillaries or lymphatics. A certain amount of fibrosis is usually present. Signs of inflammation are absent (Gates).

The metastatic carcinoma readily can be classified as either an adenocarcinoma (Fig. 211), a squamous-cell carcinoma or an undiffer-

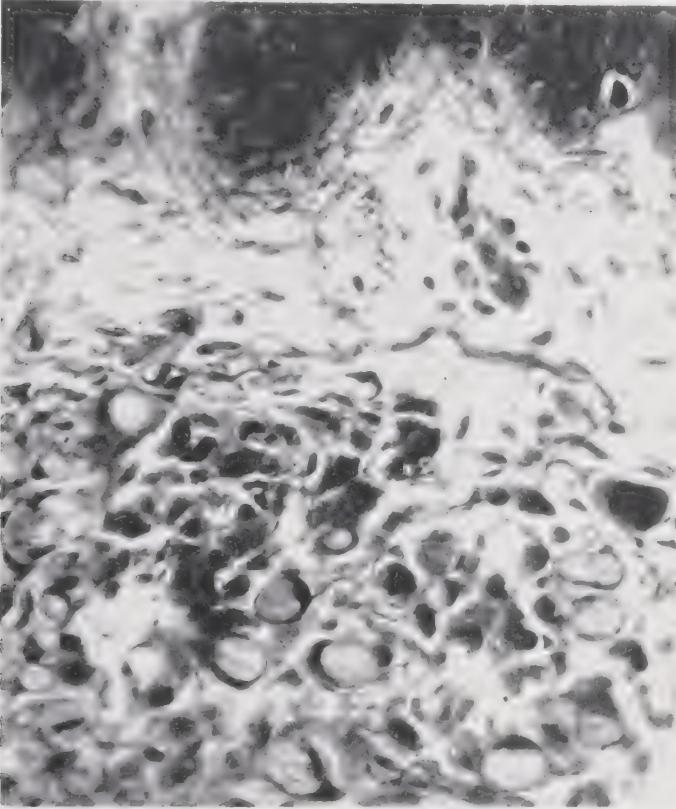


FIG. 212. Metastatic carcinoma of the skin originating from the stomach. Many of the tumor cells are so-called signet-ring cells in which, on account of the presence of mucin in the cytoplasm, the nucleus is pressed against the cell wall. ($\times 400$)

entiated carcinoma. However, it is only occasionally possible to draw conclusions from the histologic appearance of the metastasis as to the site of the primary tumor. For instance, if the tumor cells of the cutaneous metastasis contain mucin, the primary carcinoma most likely resides in the gastro-intestinal tract. The mucin-containing cells present in the metastasis appear, just as in the primary tumor, as so-called signet-ring cells—namely, as large, round cells filled with mucin which presses the nucleus against the cellular wall (Fig. 212).

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19

Mesodermal Tumors

The mesodermal tumors occurring in the skin may be divided into (1) tumors of fibrous tissue, (2) tumors of mucoid tissue, (3) tumors of fatty tissue, (4) tumors of nerve tissue, (5) tumors of vascular tissue, (6) tumors of muscular tissue and (7) tumors of osseous tissue. Inclusion of tumors of nerve tissue under mesodermal tumors is, of course, not entirely correct but appears justified because mesodermal nerve-sheath cells seem to represent an important component of most of the cutaneous tumors of nerve tissue.

Benign and malignant tumors occur. The malignant tumors of mesodermal tissue are called sarcomas. They are almost invariably single tumors. Involvement of other organs takes place by way of metastasis.

Old classifications formerly recognized spindle-cell sarcoma and round-cell sarcoma. The term spindle-cell sarcoma is synonymous with fibrosarcoma. Round-cell sarcomas are no longer classified as such but as lymphomas (i.e., stem-cell, reticulum-cell, lymphoblastic and lymphocytic lymphoma; see page 471). Lymphomas differ from sarcomas by their potentially systemic nature which is demonstrated by the fact that, frequently, they arise in multiple foci. Also, the term melanosarcoma is no longer in use, since the mother cell of the tumors formerly so designated is not a mesodermal cell. The preferred term is malignant melanoma.

1. TUMORS OF FIBROUS TISSUE

DERMATOFIBROMA, HISTIOCYTOMA (SCLEROSING HEMANGIOMA, NODULAR SUBEPIDERMAL FIBROSIS)

This lesion occurs in the skin as firm, indolent, single or multiple nodules. The nodules usually arise in adults and are situated most commonly on the extremities but occasionally elsewhere. Although they are, as a rule, not larger than a few millimeters in diameter, they may measure several centimeters in size. Most lesions have a reddish color; others are yellowish brown (because of the presence of large amounts of lipid) or bluish black (because of the presence

of large amounts of hemosiderin). In the latter case, the clinical appearance resembles that of a malignant melanoma.

Histopathology. Histologically, the nodules can be divided into two types: those composed entirely of fibroblasts (dermatofibroma) and those containing, in addition to fibroblasts, varying amounts of histiocytes (histiocytoma).

Various theories exist concerning the histogenesis of this lesion. Originally described as dermatofibroma, Woringer, in 1932, proved the presence of phagocytic histiocytes in many dermatofibromas and proposed the term histiocytoma for those containing histiocytes. He regarded histiocytomas as young dermatofibromas because of his belief that the histiocyte represents the parent cell of the fibroblast and may develop into a fibroblast (see page 33). Woringer's observations were supported by the studies of Sencar and Caro, who showed by vital staining with colloidal iron that some lesions which had histologically the appearance of dermatofibromas contained cells with phagocytic properties and thus were histiocytomas rather than dermatofibromas. Gross and Wolbach, on the other hand, have emphasized the presence of blood vessels in these lesions and have expressed their belief that they represent sclerosing hemangiomas. They regard the cells present in these lesions as proliferating endothelial cells which attempt to form new blood vessels but do not always succeed, and instead become engulfed by regressive fibrosis. It would seem, however, that the development of collagen in these tumors does not represent a regressive process but rather a progressive differentiation. A still different view has been taken by Michelson and by Rentiers and Montgomery. These authors believe that histiocytomas are not tumors at all but represent a chronic, inflammatory proliferation of fibroblasts that may follow trauma. They refer, therefore, to dermatofibroma and histiocytoma as nodular subepidermal fibrosis. The presence of histiocytes is explained by them as a response to hemorrhage and local tissue destruction.

DERMATOFIBROMA. The nodule contains varying numbers of cells, all of which are fibroblasts with spindle-shaped nuclei. Much of the collagen produced by these fibroblasts is young and instead of staining bright red with hematoxylin-eosin, it stains a pale blue, and instead of being assembled in firm bundles, it lies in individual fibers (see Plate 3). The fibroblasts and the collagen are arranged in parallel, intertwining and anastomosing bands (Fig. 213). The lesion is fairly well circumscribed, though not encapsulated, and nearly always is separated from the overlying epidermis by a narrow band of normal collagen. The epidermis may be normal or atrophic but commonly shows acanthosis with irregular downward proliferation of

the rete ridges. In some instances, this proliferation results in budding formations resembling superficial basal-cell epithelioma. The subcutaneous fat is not invaded (Rentiers and Montgomery). Evidence of phagocytic activity is lacking and staining for iron and lipid gives negative results.

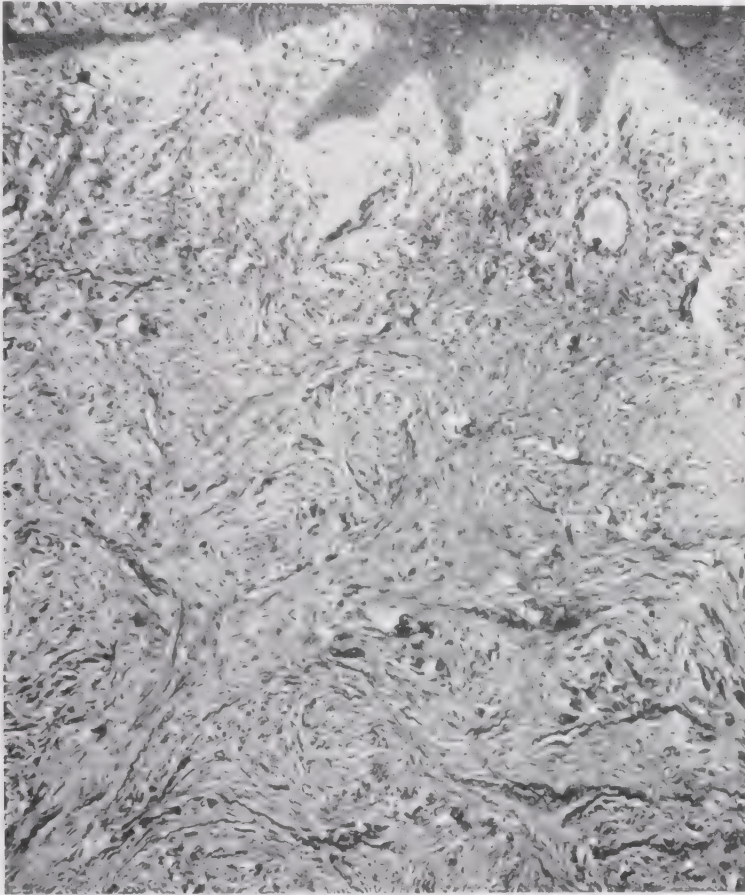


FIG. 213. **Dermatofibroma.** Low magnification. The collagen shows disorderly arrangement. Much of the collagen is young and, instead of staining bright red with hematoxylin-eosin, stains pale blue and, instead of being assembled in firm bundles, lies in individual fibers. A moderate number of fibroblasts and of capillaries are present. ($\times 50$)

HISTIOCYTOMA. In this lesion, in addition to fibroblasts, there are varying numbers of histiocytes. They tend to lie in nests. Occasionally, the great majority of cells are histiocytes. The histiocytes are larger cells than the fibroblasts and possess ample amounts of pale cytoplasm and ovoid rather than spindle-shaped nuclei (Fig. 214). Numerous newly formed capillaries with prominent endothelial cells may be present. The histiocytes contain varying amounts of lipid or

hemosiderin or both. These substances can often be recognized without special staining but are much better visualized when special stains for iron and lipid are employed. The lipid usually is doubly refractile. Some tumors contain a fairly large number of true foam cells and even Touton giant cells. Occasionally, one may find large foreign-body giant cells which have developed from either histio-

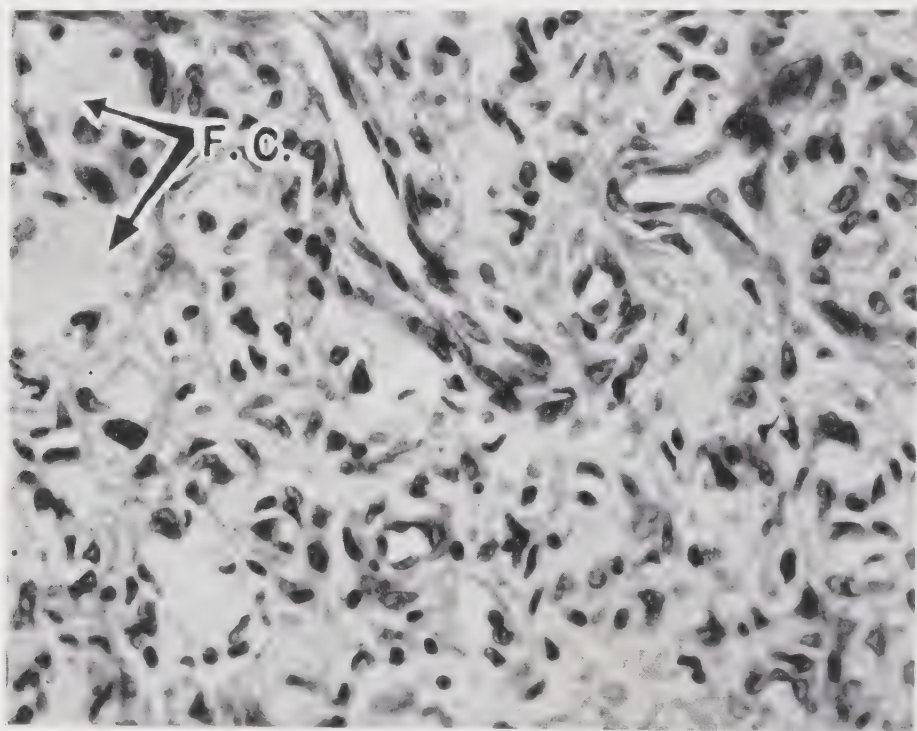


FIG. 214. **Histiocytoma.** The lesion is composed mainly of histiocytes. There are numerous large and small blood vessels lined by prominent endothelial cells. Several foam cells are present; two particularly large foam cells (F.C.) can be seen in the upper left corner. ($\times 400$)

cytes or endothelial cells (see below, under "Nevo-xantho-endothelioma," page 407).

Differential Diagnosis. In rare instances, dermatofibromas show a considerable number of nuclei. In such cases, differentiation from fibrosarcoma, especially dermatofibrosarcoma protuberans (see page 410), may cause difficulties. However, the circumscribed nature of the lesion, especially the absence of invasion into the subcutaneous fat, the lack of atypicality in the appearance of the nuclei and the absence of mitotic figures, rule out sarcoma (Michelson).

Histiocytoma with many fat cells closely resembles xanthoma tuberosum in a regressive, fibrosing stage and may even be indistinguishable from it (Arnold and Tilden). In such cases, clinical data, such as the number and the location of the lesions, and the

presence or the absence of hypercholesteremia, are necessary to arrive at the correct diagnosis.

NEVO-XANTHO-ENDOTHELIOMA

Nevo-xantho-endothelioma is characterized clinically by the presence of a group or groups of yellowish brown nodules arising in early

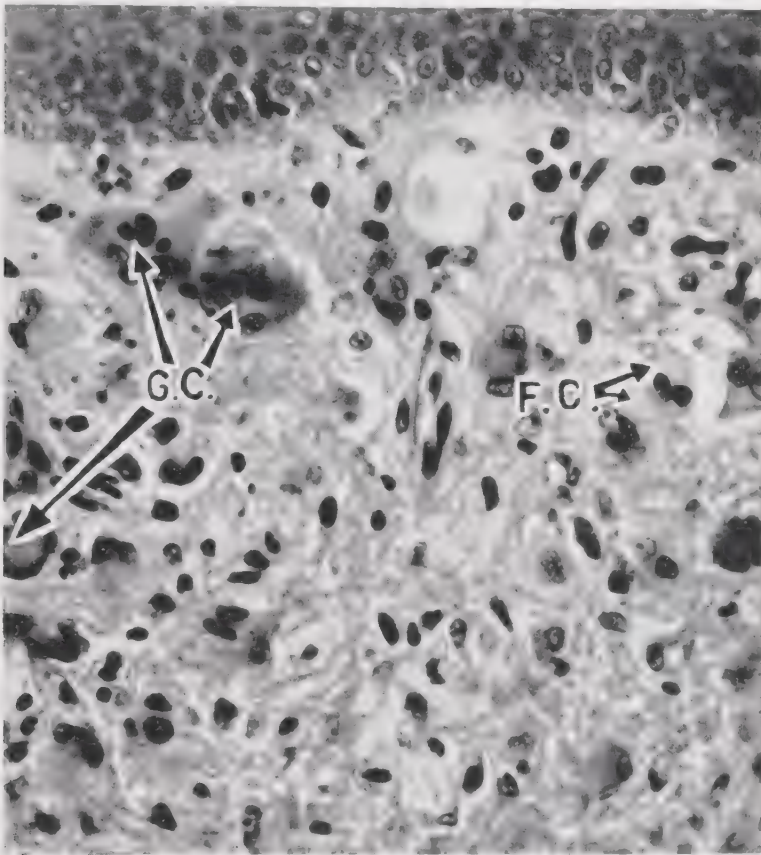


FIG. 215. Nevo-xantho-endothelioma. The lesion is composed mainly of histiocytes. Several foam cells (F.C.) and foreign-body giant cells (G.C.) are present. This lesion probably represents a form of histiocytoma. ($\times 400$)

childhood, usually on the extremities. The lesions involute spontaneously within a few years.

Histopathology. Nevo-xantho-endothelioma probably represents a young histiocytoma. As in histiocytoma, histiocytes predominate; many histiocytes have a pale, vacuolated cytoplasm and, on staining for fat, are shown to contain lipid. Typical foam cells and Touton giant cells are present. There are many capillaries showing proliferation of their endothelium. In addition, large foreign-body giant cells

are present which originate either from histiocytes or from endothelial cells (Fig. 215).

Senear and Caro and Montgomery and Osterberg regard nevo-xantho-endothelioma as a variant of xanthoma. However, since in patients with nevo-xantho-endothelioma the clinical and the blood-chemical findings do not support a diagnosis of xanthomatosis, and since the histologic picture does not differ essentially from that of histiocytoma, it seems best to regard the lesion as a histiocytoma. Nevo-xantho-endothelioma differs from histiocytoma only by showing foam cells and giant cells of the foreign-body type in larger number.

RETICULO-HISTIOCYTOMA

This rare condition occurs as solitary or multiple, fairly large cutaneous nodules in adults. The lesions may remain stationary or may involute.

Histopathology. The histologic picture is characterized by the presence of large, bizarre-shaped, multinucleated giant cells with abundant, pale cytoplasm and vesicular nuclei. They are separated from one another by fibrous connective tissue (Zak). Occasionally, it is possible to demonstrate the presence of fat within the cytoplasm of these cells. Vital staining with colloidal iron indicates that the large cells have phagocytic properties and are reticulo-endothelial in nature (Caro and Senear).

It is likely that reticulo-histiocytoma is an unusual type of histiocytoma. Caro and Senear assume that it is not a true neoplasm but actually a granuloma.

KELOID

Keloids represent a post-traumatic tissue proliferation. They are red, raised and firm, and have a smooth, shiny surface. Occasionally, clawlike projections radiate from the edges of the lesions.

Histopathology. Keloids cannot be differentiated from a dermatofibroma on a histologic basis. In an early keloid, one finds, in addition to thick, intertwining bundles of collagen, a moderate number of fibroblasts (Fig. 216). An old keloid may show but few cellular elements.

FIBROSARCOMA

Fibrosarcoma occurs in the skin in two forms: as true fibrosarcoma and as dermatofibrosarcoma protuberans. However, there is justifiable doubt that the latter represents a real sarcoma.

TRUE FIBROSARCOMA

True fibrosarcoma starts only rarely in the dermis; more commonly, it starts in the subcutaneous fat (Broders, Hargrave and

Meyerding). The tumor usually feels firm and irregular on palpation and at first is covered by normal skin. It usually grows quite rapidly and as it increases in size the overlying skin at first shows purplish discoloration and finally ulceration. Satellite lesions frequently develop. Metastases occur sooner or later. They usually spread by way of the blood stream, especially to the lungs. The regional lymph nodes are involved only rarely (Gentele).



FIG. 216. **Keloid.** The lesion is composed of thick, intertwinning bundles of collagen. The collagen is entirely mature and stains eosinophilic throughout. A moderate number of nuclei are present; therefore, this keloid is of relatively recent genesis. ($\times 200$)

Histopathology. This tumor is very cellular. The nuclei vary greatly in size, shape and staining qualities. Although most nuclei are spindle-shaped, others appear round or oval. Some nuclei stain very dark, while others appear vesicular with irregular chromatin structure. Typical as well as atypical mitotic figures are present, often in large numbers. The nuclei tend to lie in bundles that extend in various directions but do not form whorls. In some areas, the nuclei lie in dense clusters. Thus, fibrosarcomas present an extremely disorderly arrangement of the nuclei. Usually, these tumors contain some collagenous tissue, in which the nuclei appear to be embedded,

but highly malignant fibrosarcomas may possess little or no collagen. Instead, on staining with a reticulum stain, they are seen to contain numerous reticulum fibers (Foot).

Because of the invasive nature of these tumors, ulceration at the surface and infiltration into the subcutaneous tissue and underlying structures frequently are observed.

Differential Diagnosis. A highly malignant fibrosarcoma with no production of collagen may be difficult to differentiate from squamous-cell carcinoma, Grade IV, amelanotic malignant melanoma, stem-cell lymphoma or reticulum-cell lymphoma. On thorough inspection, however, one will usually find, in squamous-cell carcinoma, Grade IV, some tendency to keratinization and connections of the tumor with the epidermis (page 331); in malignant melanoma, one will find "junction activity" at the epidermo-dermal border (page 458); while in stem-cell and reticulum-cell lymphoma spindle-shaped nuclear forms are absent, since all cells are "round cells" (see pages 474, 475).

Spindle-celled malignant tumors may form in areas of radiodermatitis. Although they have the morphologic appearance of a fibrosarcoma, it is likely that most, if not all, represent Grade IV spindle-celled squamous-cell carcinoma (see page 333) (Gentele; Blom-Ides).

DERMATOFIBROSARCOMA PROTUBERANS

Dermatofibrosarcoma protuberans represents a slowly growing tumor which has its origin in the dermis. It begins with one or several closely set, small, hard nodules, which are reddish or bluish. As the nodules coalesce, they form one or several plaques. On these plaques, protruding tumors subsequently develop and may ulcerate.

Although this tumor is locally invasive, as a rule, it does not give rise to metastases. In exceptional cases, metastases may occur many years after the appearance of the tumor. Binkley, for instance, reported a case in which metastases caused the death of the patient 38 years after the tumor had first appeared. Costa has expressed the belief that dermatofibrosarcoma protuberans was not truly malignant because of its slow rate of growth and the absence of metastases in most cases. He regards the tumor as intermediary between dermatofibroma and true fibrosarcoma, partaking of the nature of both. He prefers to call it progressive recurrent dermatofibroma.

Histopathology. The histologic appearance of the tumor does not differ materially from that of true fibrosarcoma (Binkley). A differentiation of the two tumors on a histologic basis, therefore, is not always possible. Just as in true fibrosarcoma, the nuclei lie in irregu-

lar bands; but, in addition, they also form whorls (Fig. 217). Furthermore, they show less atypicality and are more uniformly fusiform. Formation of collagen is usually well in evidence. Thus, the fibroblastic nature of the tumor is always recognized easily. Mucoid degeneration of the collagen is observed commonly in parts of the tumor (Binkley). Ulceration at the surface and invasion into the subcutaneous fat occur.

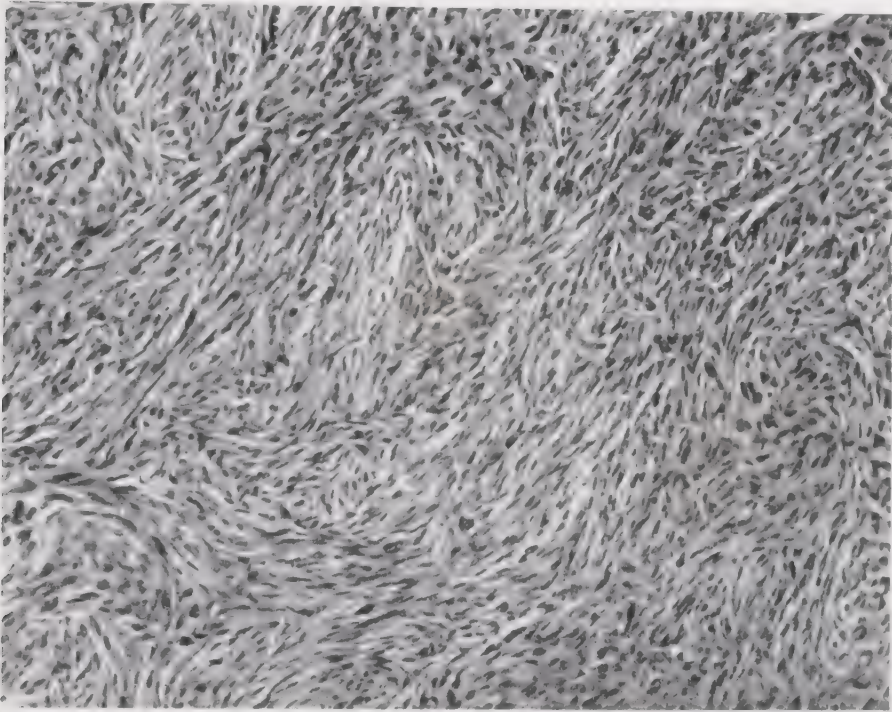


FIG. 217. *Dermatofibrosarcoma protuberans*. The nuclei of the fibroblasts are arranged in irregular strands and whorls. They show a slight degree of atypicality. In contrast with malignant fibrosarcoma, formation of collagen is well in evidence. ($\times 200$)

Differential Diagnosis. For differentiation from dermatofibroma, see page 406.

2. TUMORS OF MUCOID TISSUE

MYXOMA

Although fibromas and neurofibromas may undergo more or less complete mucoid degeneration and then present in such degenerated areas the aspect of myxoma, myxomas may arise as such.

Clinically, myxomas present themselves as fairly well circumscribed, rather soft, usually intracutaneous tumors over which the epidermis is normal.

Histopathology. Myxomas contain embryonal fibroblasts that possess the ability to produce mucin in a manner similar to that of the embryonal fibroblasts of the umbilical cord. The number of these cells in myxomas is usually small. Those present are spindle-shaped or stellate cells possessing multipolar processes. The stroma appears homogeneous and gelatinous. It stains pale blue with hematoxylin

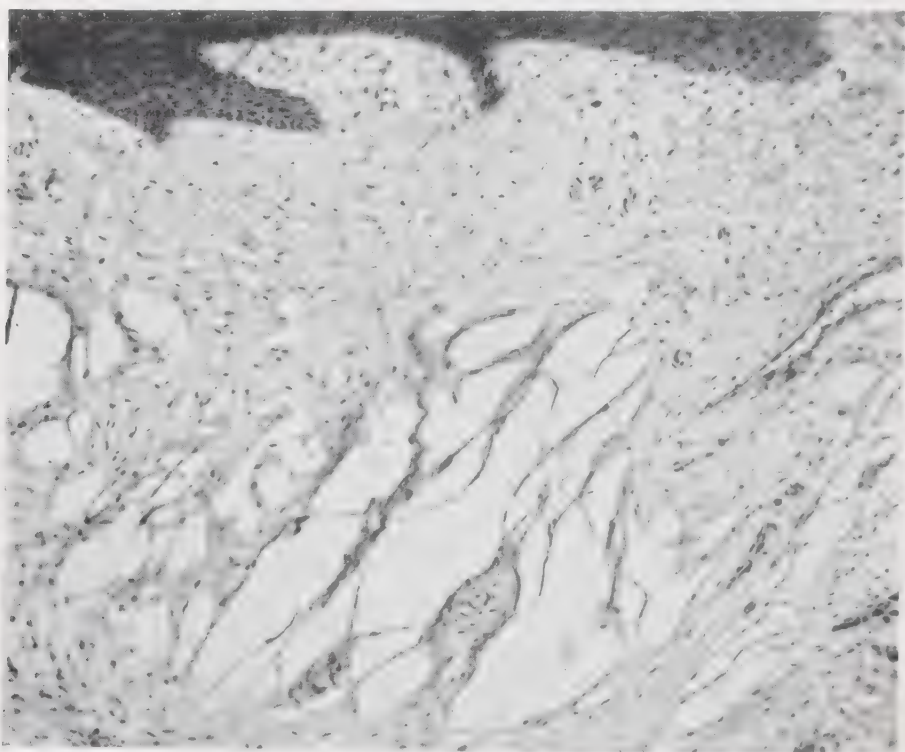


FIG. 218. **Myxoma.** The stroma appears homogeneous and in some places gelatinous. The empty spaces are caused by shrinkage of the mucin in the process of fixation. ($\times 200$)

and eosin, and red with Best's mucicarmine stain. Because of shrinkage in the process of fixation, empty, cleftlike spaces frequently are observed in the stroma (Fig. 218).

Many myxomas are not pure but contain other mesodermal elements. Thus, fibromyxomas and lipomyxomas occur.

MYXOSARCOMA

Clinically, myxosarcomas are, as a rule, primarily subcutaneous tumors which, as they grow in size, may cause ulceration of the skin.

Histopathology. A decision whether a tumor represents a myxoma or a myxosarcoma is often difficult. A high degree of cellularity and

atypicality of the cells favor a diagnosis of myxosarcoma. The cells tend to be stellate and multipolar.

SYNOVIAL CYST OF THE SKIN (MYXOMATOUS DEGENERATION CYST OF THE SKIN)

This lesion occurs most commonly on the hands, particularly near the terminal interphalangeal joints. The lesion consists of a small, semiglobular, translucent tumor surrounded by erythema. When punctured, a clear, mucinous fluid exudes.

Histopathology. Histologic examination reveals a cystic cavity in the dermis or the subcutaneous tissue. The lining wall is made up of fibrous tissue and shows no endothelial or epithelial lining. The cyst is filled with mucoid material.

The histogenesis is not clear. MacKee and Andrews regarded the lesion as a synovial cyst. Savatard held that the lesion formed because of mucoid degeneration of a fibroma. Woodburne stated that he had never seen any evidence of a previously existing solid tumor. He expressed the belief that the lesion arises because of myxomatous degeneration of fibrous tissue of the dermis or of other fibrous tissue.

3. TUMORS OF FATTY TISSUE

LIPOMA

Lipomas occur as single or multiple, subcutaneous, soft, rounded, lobulated growths which may or may not be movable against the overlying skin. In rare instances, multiple lipomas have been reported as present, not only in the subcutaneous but also in the visceral fat depots. This condition is known as systemic multicentric lipoblastosis (Tedeschi).

Histopathology. Lipomas are composed of fat cells and may or may not be surrounded by a connective-tissue capsule. The fat cells in lipomas usually do not differ from normal fat cells. Occasionally, they are slightly larger. In some lipomas there is more, in others less, of a connective-tissue framework than in normal subcutaneous fat. Those containing a considerable proportion of connective tissue are called fibrolipomas.

Systemic multicentric lipoblastosis shows not only adult fat cells, as lipomas do, but also embryonal fat cells and undifferentiated mesenchymal cells, with all intermediate stages. These lesions are hamartomas, analogous to the lesions of von Recklinghausen's disease, and not sarcomas. They show no cellular disorder and no mitotic figures (Tedeschi).

HIBERNOMA

Hibernoma is a rare, benign, solitary, soft, subcutaneous tumor which may slowly increase in size. Clinically, it is indistinguishable from lipoma.

Histopathology. The tumor is composed largely of multilocular fat cells which resemble those occurring as brown fat in the hibernating gland of hibernating animals. However, since multilocular fat cells resembling those of brown fat may occur as a transitory phase in the maturation of ordinary, yellow adipose tissue, it is possible that hibernoma merely represents a tumor of embryonal yellow fat cells (Sutherland).

Histologic examination reveals a lobulated tumor composed predominantly of closely spaced, round or oval cells with a distinct cell membrane and centrally placed nucleus. The cells contain either granules or small vacuoles or locules which stain positive with fat stains. This fat is, in contrast with mature fat, doubly refractile to polarized light (Sutherland). In some multilocular cells, coalescence of smaller into larger locules can be seen, with eccentric displacement of the nucleus. There are, in addition, a few unilocular, normal mature fat cells which are larger than the granular and multilocular cells. There thus seems to be evidence of a transition from granular to multilocular and even to unilocular fat cells (Brines and Johnson).

Differential Diagnosis. The tumor can be differentiated from malignant hibernoma by its regular architecture and the absence of mitotic figures and multinucleated cells.

LIPOSARCOMA

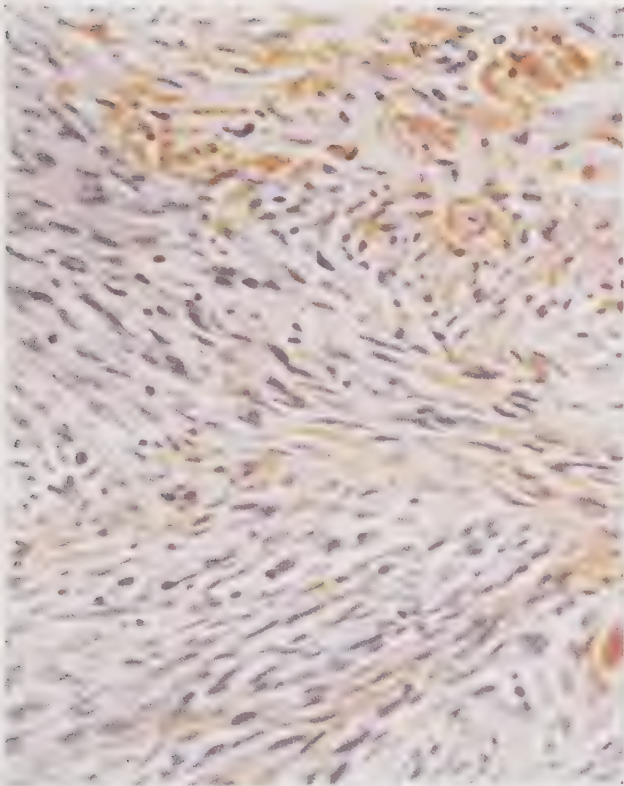
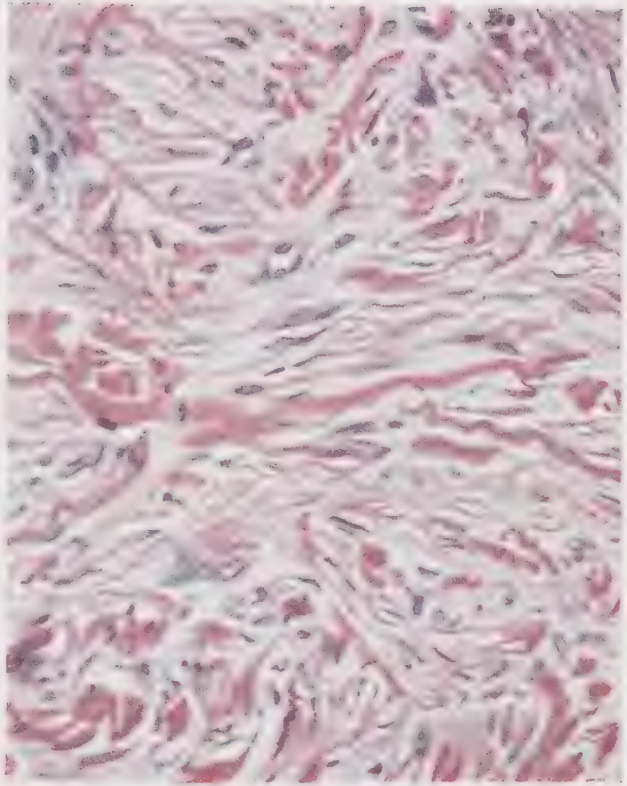
Liposarcomas, as a rule, arise *de novo*, but they may develop within a pre-existing lipoma (Sternberg). They not only occur in the subcutaneous fat but also may be found wherever there is fatty tissue. Those located in the subcutaneous fat present themselves as diffuse nodular infiltrations. Metastases are common, especially to the lungs and the liver.

Histopathology. The histologic picture varies somewhat with the degree of malignancy. Moderately malignant tumors are easily recognizable as fatty tumors, while very malignant ones may not be identifiable as such unless fat stains are employed.

A moderately malignant liposarcoma consists of adult fat cells and moderately atypical immature fat cells (lipoblasts). The latter have a spindle-shaped or stellate nucleus and contain fat droplets in their

PLATE 3

Dermatofibroma. Most of the collagen is young and stains faintly basophilic instead of deeply eosinophilic as the mature collagen does. Several capillaries lined by large endothelial cells are present. ($\times 175$)



Kaposi's sarcoma. A fibroblastic area is shown. Numerous extravasated erythrocytes lie among the fibroblasts.

cytoplasm (Fig. 219). There is a loose meshwork of connective tissue which usually but not always is mucoid (Stout).

A highly malignant liposarcoma contains highly atypical lipoblasts with bizarre nuclei. The amount of fat in them is often small. There are areas which resemble fibrosarcoma. The stroma usually is mucoid.

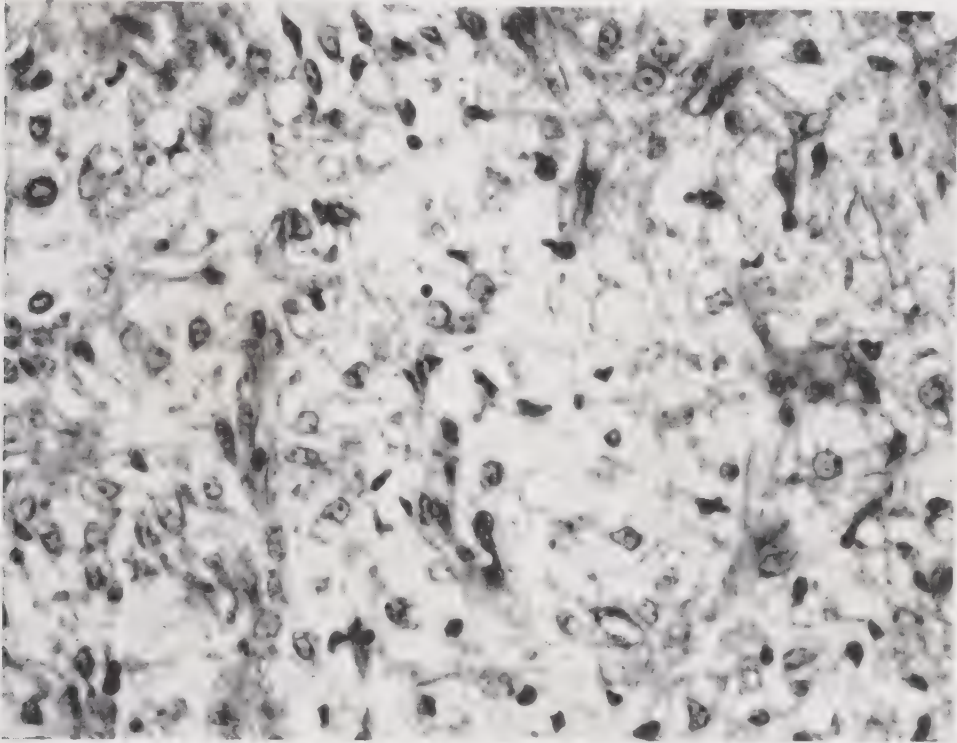


FIG. 219. **Liposarcoma.** The tumor is composed predominantly of moderately atypical, immature fat cells (lipoblasts) but contains also a few adult fat cells. Their presence aids in the diagnosis. There is a moderate amount of loose, mucoid connective tissue. ($\times 400$)

MALIGNANT HIBERNOMA

The clinical appearance of malignant hibernoma is the same as that of other liposarcomas.

Histopathology. The cells comprising this tumor are rounded, have a centrally placed nucleus and contain numerous, small and large vacuoles of fat in their cytoplasm. Those containing large vacuoles are called mulberry cells. Some of the cells are of very large size and contain multiple, bizarre nuclei (Fig. 220). The cells of this tumor lie close together so that there is hardly any stroma (Stout).

Combinations of liposarcoma and malignant hibernoma occur.

Stout regards this as evidence that ordinary adipose tissue and brown fat come from the same ancestral lipoblastic cell.

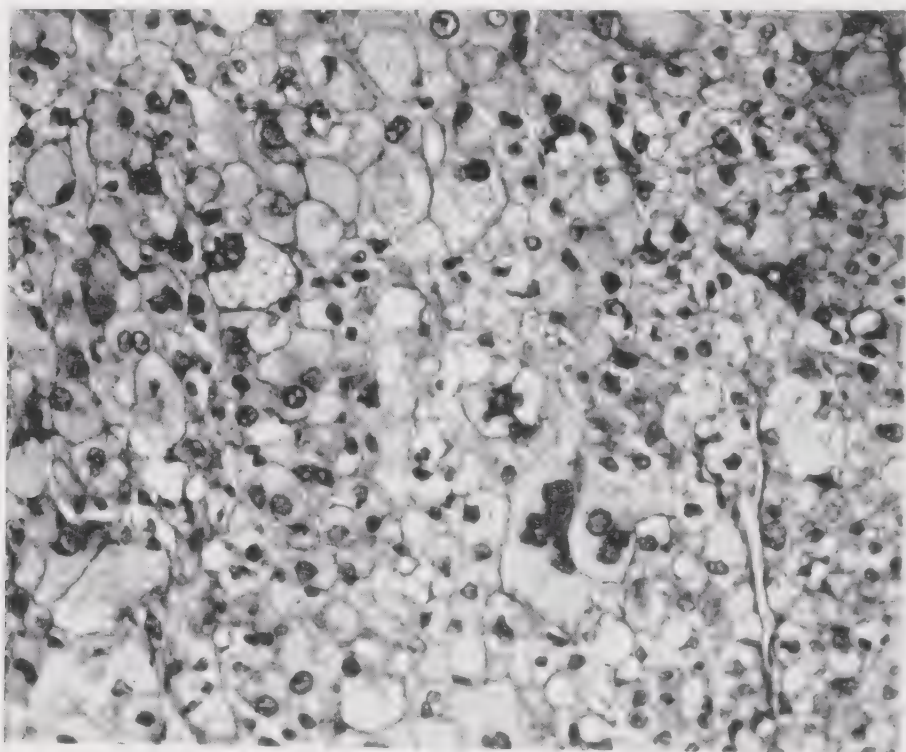


FIG. 220. Malignant hibernoma. The fat cells contain bizarre nuclei and are filled with small and large vacuoles of fat. Those containing large vacuoles are called mulberry cells. There is hardly any stroma. ($\times 200$)

4. TUMORS OF NERVE TISSUE

Three types of nerve tumors may occur in the skin: neuroma, neurofibroma and neurolemoma.

NEUROMA

Neuromas nearly always occur as single tumors secondary to an injury of a nerve. In rare instances, they occur as single (Duemling) or multiple (Ludy) tumors, apparently without preceding nerve injury. Neuromas are small, reddish nodules which may or may not be painful.

Histopathology. In their histologic appearance, neuromas resemble the amputation neuromas, which represent a hyperplasia of nerves and are not tumors. For this reason, Ludy preferred to regard also the nontraumatic neuromas of the skin as neuromatoid hyperplasia.

Neuromas show numerous thick bundles of medullated nerves in the dermis, extending in different directions. Thus, some bundles

appear cut in transverse and others in longitudinal direction (Fig. 221). Each nerve bundle is surrounded by fibrous tissue.

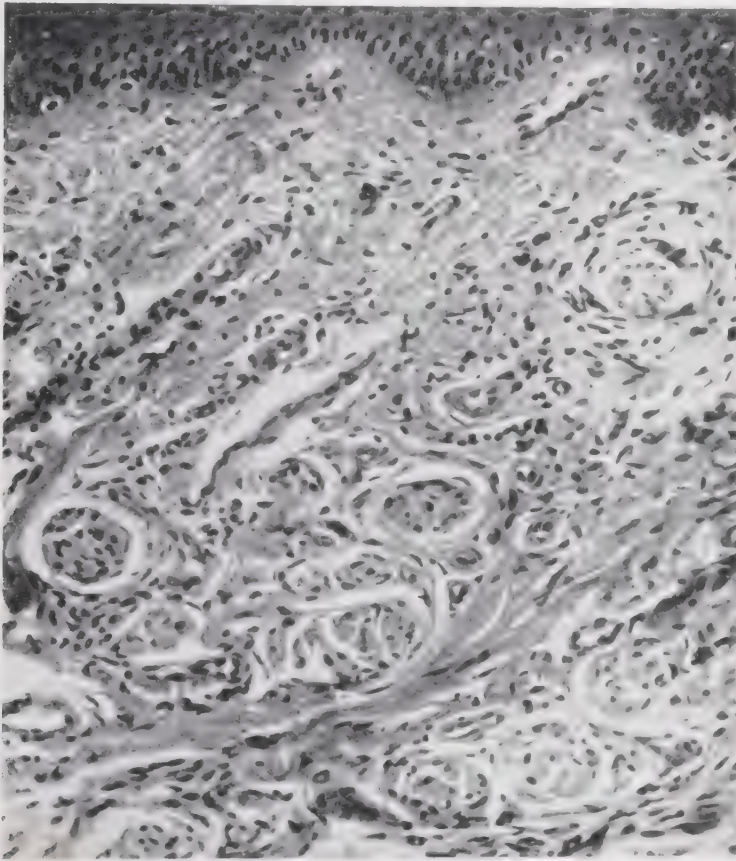


FIG. 221. **Neuroma.** Numerous thick bundles of medullated nerves are present. Each nerve bundle is surrounded by fibrous tissue. ($\times 200$)

NEUROFIBROMATOSIS (VON RECKLINGHAUSEN'S DISEASE)

Neurofibromatosis is characterized by the presence of multiple cutaneous tumors which possess a characteristic soft consistency and usually are flesh-colored, but may be brownish or violaceous. The lesions are semiglobular or pedunculated and vary considerably in size. Occasionally, large, pendulous, flabby masses weighing a pound or more are encountered. In most cases, in addition to the tumors, the skin shows yellowish brown pigmented macules of various size and shape—so-called café-au-lait spots.

Histogenesis. Neurofibromas are tumors of nerve sheaths. Normally, each neurite or axon, whether myelinated or not, is surrounded by a neuro-ectodermal sheath, the schwannian sheath, and

a mesodermal sheath, the endoneurium (see page 22). It is still a matter of controversy whether the cells composing neurofibromas represent neuro-ectodermal schwannian cells or mesodermal endoneurial cells. Whereas von Recklinghausen originally regarded the tumors as derived from the connective tissue of nerves, Verocay, in 1910, first suggested that the cells of the tumors were immature cells

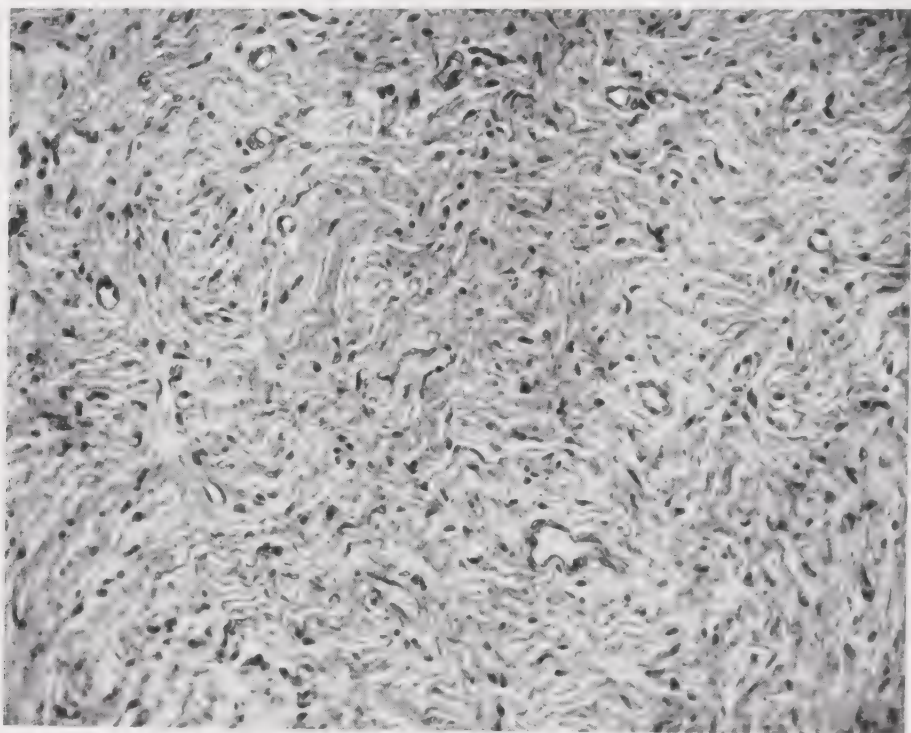


FIG. 222. Neurofibroma (von Recklinghausen's disease). The tumor is composed of wavy fibrils of young collagen which lie loosely together and tend to form eddies and whorls. The young collagen stains pale blue with hematoxylin-eosin. ($\times 200$)

of the sheath of Schwann and thus neuro-ectodermal cells. He suggested that the tumors be called neurinomas. Among more recent writers on the subject, some (Murray and Stout) subscribe to Verocay's view. Others (Penfield; Tarlov) still adhere to the view that the tumors develop from the perineural connective tissue. Many more recent authors, however, feel that probably both ectodermal schwannian sheath cells and perineural connective-tissue cells participate in the formation of the tumors (Foot; McNairy and Montgomery). Masson, who observed that neural elements were conspicuous in young tumors but sparse or absent in old tumors concluded that neurofibromas basically were neural tumors. However, with aging, the neural elements gradually degenerated and were replaced by connective-tissue proliferation.

It is unfortunate that the schwannian cell and the endoneurial fibroblast cannot be differentiated by present histologic methods. Since the schwannian cell can also produce reticulum fibers and collagen (Masson; Murray and Stout), the presence of these structures in neurofibromas does not decide the issue. Murray and Stout believe that their findings in tissue cultures favor the schwannian origin of

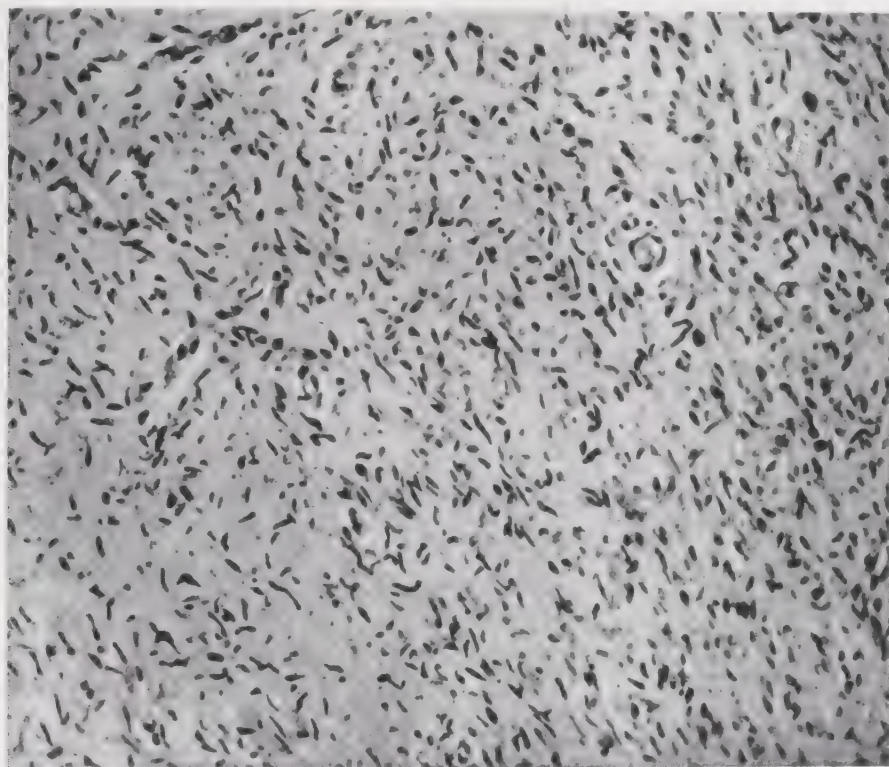


FIG. 223. Neurofibroma (von Recklinghausen's disease). In this tumor, mucoid degeneration of the collagen has taken place. This is a not uncommon occurrence in lesions of neurofibroma. ($\times 200$)

neurofibroma, because the mode of outgrowth of schwannian cells from normal nerves and of cells in neurofibroma is very similar.

Histopathology. Histologic examination of the cutaneous tumors shows them to be well circumscribed but not encapsulated. The tumor masses often extend into the subcutaneous fat. They are composed of wavy fibrils which lie in loose strands and tend to form eddies and whorls. The loose-textured, wavy arrangement of the fibrils is characteristic of neurofibroma (Fig. 222). With hematoxylin-eosin, the fibrils usually stain pale blue like young collagen and not pink like mature collagen. Some tumors contain a certain amount of mature, pink-staining collagen. Embedded between the fibrils one finds a fairly large number of nuclei which are oval or spindle-shaped,

uniform in size and rather pale-staining. Elastic fibers are absent in the tumors. On staining with Foot's stain, numerous wavy reticulum fibers are seen. In most neurofibromas, a few nonmedullated, thin, long nerve fibers can be recognized on staining with special nerve stains, such as Bodian's stain (McNairy and Montgomery).

Not infrequently, mucoid degeneration of the collagen is observed in parts of a tumor or in an entire tumor. In such cases, the nuclei

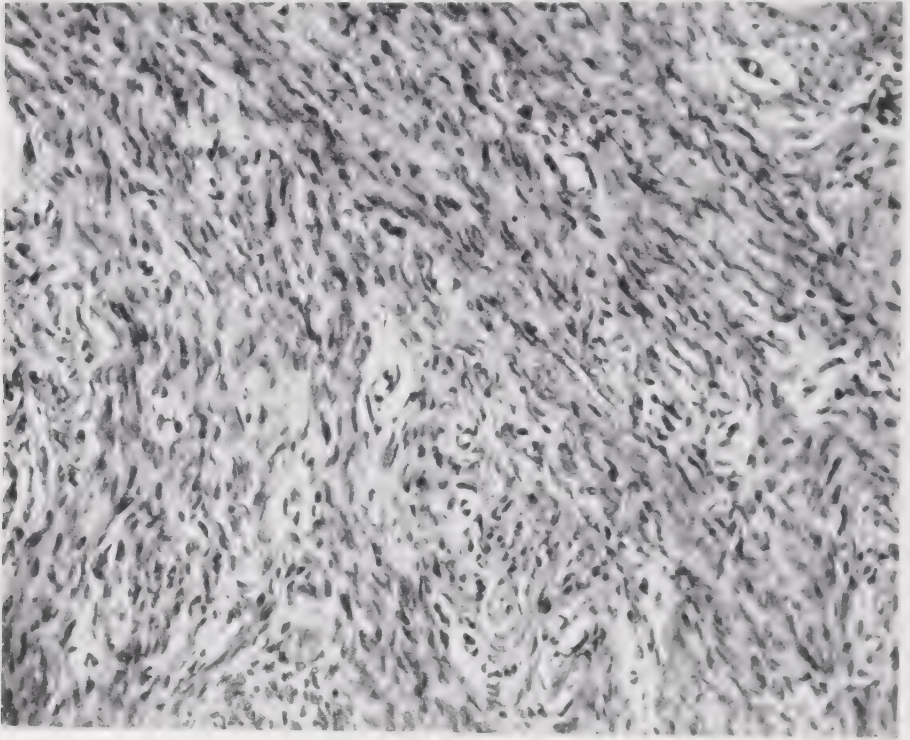


FIG. 224. Neurofibrosarcoma (von Recklinghausen's disease). The wavy pattern characteristic of neurofibroma is preserved, but the nuclei are increased in number and are atypical. ($\times 200$)

are embedded in a homogeneous, pale-blue ground substance (Fig. 223). One must be familiar with this change, because it results in a histologic picture quite different from that usually associated with neurofibroma.

The pigmented macular lesions seen in neurofibromatosis, the so-called café-au-lait spots, merely show increased melanin pigmentation in the basal layer.

Systemic Lesions. There may be tumors of the central and peripheral nervous systems, of the viscera (Grill and Kuzma) and of the bones. Involvement of a bone may lead either to extensive destruction or to hypertrophy of bony tissue (Westcott and Ackerman).

Malignant Degeneration. Malignant degeneration of neurofibromas of the skin is rare. In tumors of the central and the peripheral

nervous systems and of the bones, however, it is a not uncommon occurrence. Hosoi, in 1931, found 65 instances of malignant degeneration reported in the literature; he stated that this represented 13 per cent of all the reported cases of neurofibromas. The conclusion drawn by Charache that "sarcomatous transformation is present in 13 per cent of all cases of multiple neurofibroma" is not justified, however, because in neurofibromatosis, as in other common diseases, exceptional cases are reported more often than ordinary ones.

Most malignant tumors in neurofibromatosis appear like ordinary fibrosarcomas and give no indication of their origin from a neurofibroma. In some, however, the pattern of a neurofibroma is preserved: there is still a wavy arrangement of the collagen fibrils, but the nuclei are increased in number and are atypical (Fig. 224). Nerve fibers are never found (Stout; Wachstein and Wolf).

NEUROLEMOMA

Neurolemoma occurs as either solitary or multiple tumors but not as a systematized disease like neurofibromatosis. The lesions which are asymptomatic are found in the dermis or in the subcutaneous tissue. They can reach a diameter of several centimeters and undergo

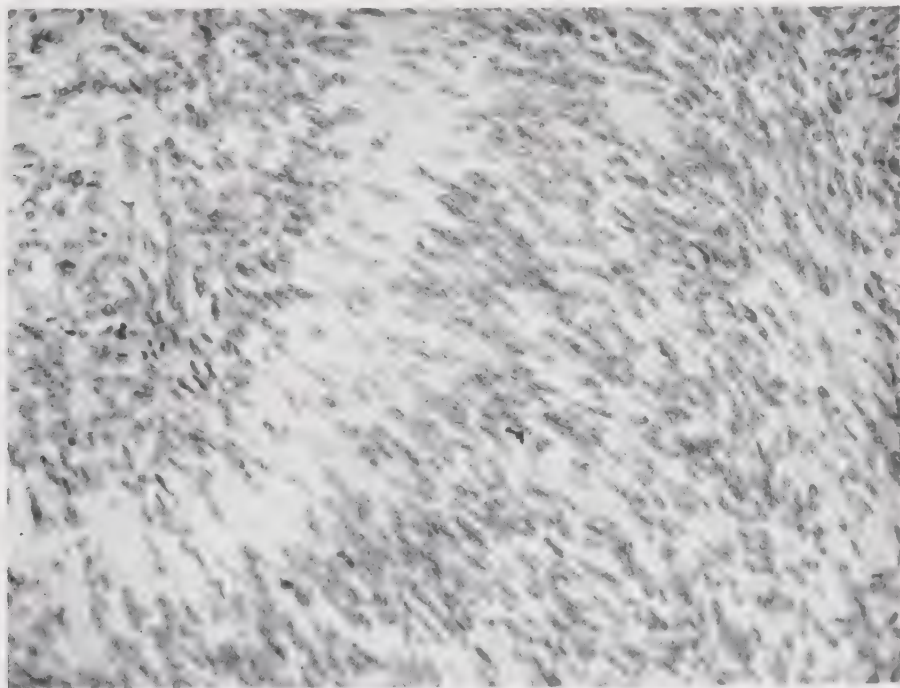


FIG. 225. **Neurolemoma.** Numerous elongated nuclei are arranged in a streaming fashion. In the center of the field lies a so-called Verocay body formed by a double palisade of nuclei enclosing a space nearly devoid of nuclei. ($\times 200$)

partial cystic degeneration. Malignant degeneration does not occur, however.

Histopathology. The tumor arises from the sheath of Schwann of a peripheral nerve and is composed of schwannian cells. It is well encapsulated. One observes numerous bands of closely spaced, elongated nuclei arranged in a twisting, streaming fashion. Here and there, the nuclei lie in two rows or palisades enclosing a space nearly devoid of nuclei. Such formations are called Verocay bodies (Fig. 225). In addition to these areas of streaming and palisading, there are areas in which the schwannian cells are embedded in a loose meshwork of fine connective-tissue fibers. Small cysts may be present which by coalescence may form gross cystic spaces (Stout). No nerve fibers are found in neurolemoma. Mast cells often are present in conspicuous numbers.

5. TUMORS OF VASCULAR TISSUE

HEMANGIOMA

Hemangiomas may be divided into three clinical types: (1) nevus flammeus (port-wine nevus), (2) nevus vasculosus (strawberry mark) and (3) angioma cavernosum.

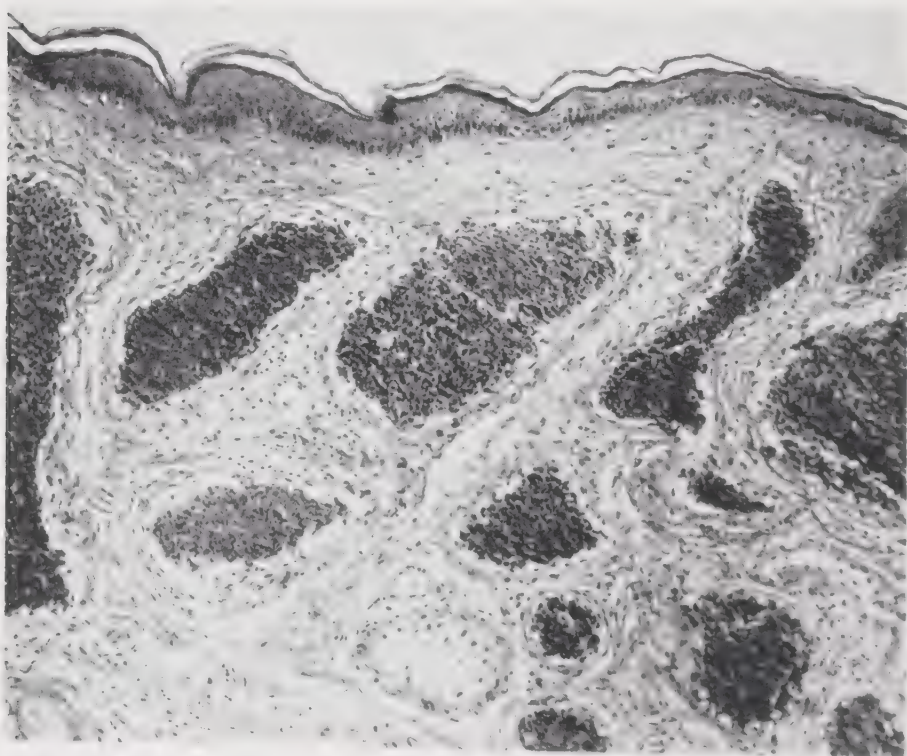


FIG. 226. Hemangioma (nevus flammeus). The capillaries are increased in number. They are dilated, engorged with blood and lined by only a single layer of endothelial cells. ($\times 100$)

Nevus flammeus is characterized by one or several dull-red or bluish red patches of irregular outline, not elevated above the level of the skin.

Nevus vasculosus is a raised, bright-red, soft, often lobulated tumor. When lobulated, its appearance resembles that of a strawberry.

Cavernous hemangioma consists of a large, soft, subcutaneous mass. If, as is often the case, the lesion is located on the face, consid-

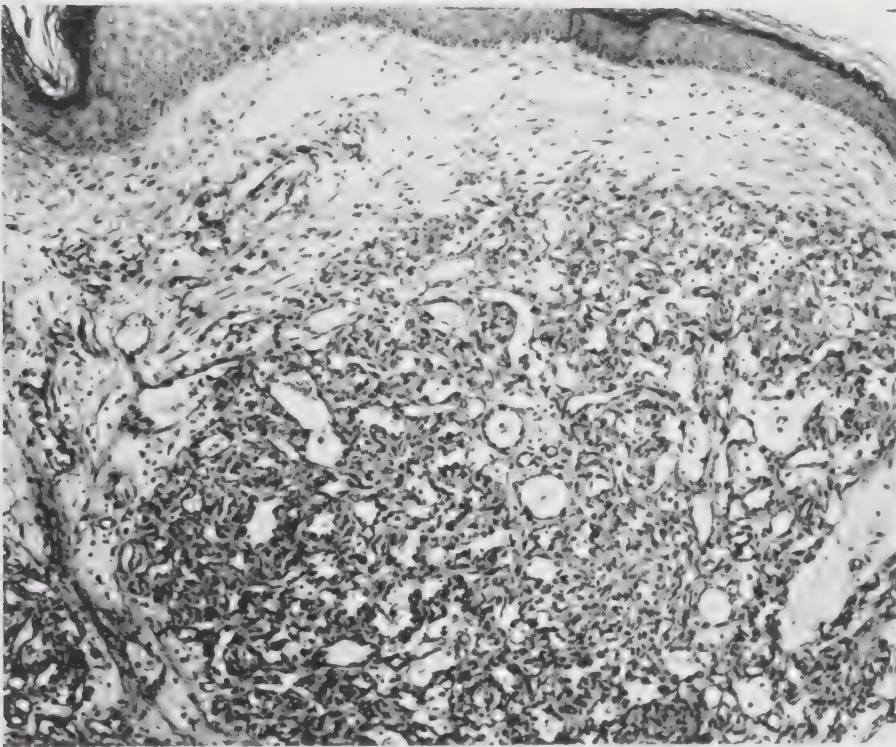


FIG. 227. Hemangioma (nevus vasculosus). There are numerous dilated capillaries with considerable proliferation of their endothelial cells. ($\times 100$)

erable deformity may result. The overlying skin may be normal but often is the site of a nevus vasculosus.

Histopathology. NEVUS FLAMMEUS shows dilatation and an increase in the number of capillaries in the dermis (Miescher). No proliferation of endothelial cells is present (Fig. 226).

NEVUS VASCULOSUS, which represents a capillary hemangioma, in addition to marked increase and dilatation of the capillaries, shows considerable proliferation of endothelial cells (Fig. 227). In areas of proliferation, the endothelial cells are large and lie in several layers around capillary lumina. In addition, they form solid strands and masses with little evidence of vascular lumina.

CAVERNOUS HEMANGIOMA shows in the lower dermis and in the subcutaneous tissue large, irregular spaces filled with blood. They

are lined by a single layer of thin endothelial cells and by thick walls (Fig. 228). The thickening is produced mainly by overgrowth of adventitial cells.

Sclerosing hemangioma, since it is a dermatofibroma rather than an angioma, is discussed under "Dermatofibroma" (see page 403).

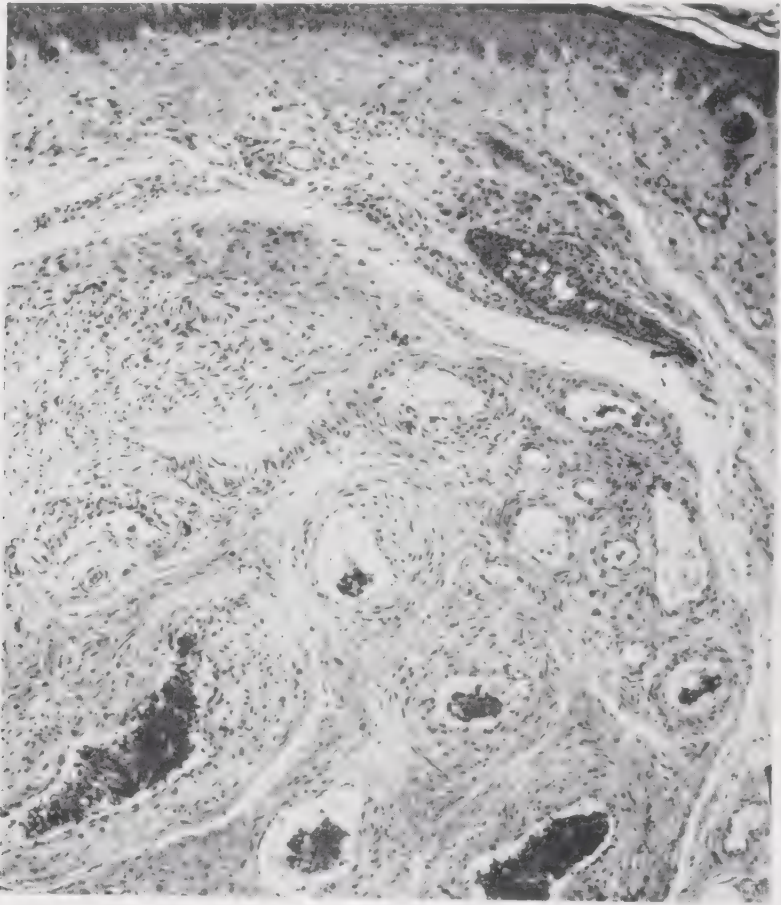


FIG. 228. Hemangioma (hemangioma cavernosum). The blood vessels show considerable thickening of their walls produced by overgrowth of adventitial cells. ($\times 100$)

GRANULOMA PYOGENICUM

This lesion, which usually is single, consists of a dull-red, soft or fleshy, raised, more or less pedunculated nodule. Its size varies from 0.5 to 2 cm. in diameter. The surface may show a smooth, atrophic epidermis but often is covered by crusts. The lesion bleeds easily when traumatized.

Histopathology. On histologic examination, one finds a circumscribed, raised, pedunculated lesion covered by a flattened epidermis and containing numerous newly formed capillaries showing varying

degrees of dilatation (Fig. 229). A slight to moderate amount of endothelial proliferation is usually present. The capillaries are embedded in a loose, edematous, occasionally mucoid, connective tissue. At the neck of the pedunculated lesion, the epidermis usually shows acanthotic inward growth, thus forming a so-called epidermal collarette.

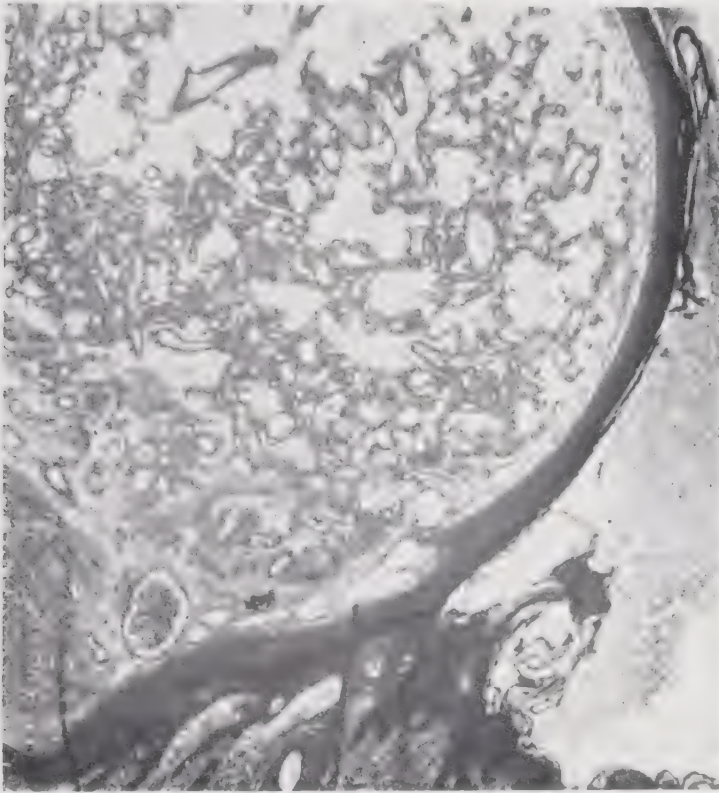


FIG. 229. Granuloma pyogenicum. The lesion is pedunculated. It is composed of numerous capillaries embedded in a loose, edematous stroma. No inflammatory reaction is present. ($\times 50$)

In early lesions, one finds no inflammatory reaction (Freund). In older lesions, because of the fact that the thinned epidermis usually erodes, secondary inflammatory changes are often present in the stroma and may give the tumor a granulomatous appearance.

There is no agreement whether this lesion represents a granuloma caused by a pyogenic infection or a hemangioma. The histologic picture favors the latter view. Freund has pointed out that, even when the lesion shows a marked granulomatous reaction, the center still retains the appearance of a typical hemangioma.

Differential Diagnosis. Differentiation from nevus vasculosus, which also represents a capillary hemangioma, is usually easy because

of the raised pedunculated growth of the lesion, the presence of edema or mucoid degeneration in the stroma, the thinning of the epidermis over the tumor and the collarette formation of the epidermis at the neck of the tumor.

ANGIOKERATOMA MIBELLI, ANGIOKERATOMA CORPORIS DIFFUSUM

In angiokeratoma Mibelli, one observes on the dorsum of the fingers, on the toes and on the knees from pinhead- to bean-sized, dark-red, vascular papules with a verrucous surface. The disease arises in young subjects.

In angiokeratoma corporis diffusum, dark-red, vascular papules are present in great number over the entire trunk. They are smaller and show less hyperkeratosis than those of angiokeratoma Mibelli. Angiokeratoma corporis diffusum may be associated with internal lesions such as swelling and vacuolation of the muscle fibers of the blood vessels and of the heart (Ruiter).

Histopathology. Histologic examination of the cutaneous lesions reveals in both diseases telangiectasias of superficial location associated with changes in the epidermis consisting of hyperkeratosis, acanthosis, irregular proliferation of the rete ridges and papillomatosis. Greatly dilated capillaries lined by a thin layer of endothelial cells lie in the papillae and are partly or completely surrounded by the hypertrophic stratum malpighii. If completely surrounded, the dilated capillaries have the appearance of intra-epidermal "blood cysts." Some of the blood cysts may have lost their endothelial lining. Atrophy of the stratum malpighii may occur directly over blood cysts because of the pressure which the cysts exert on the overlying epidermis.

SENILE HEMANGIOMA

Senile hemangiomas are small, raised, soft, dark-red nodules, measuring usually between 1 and 3 mm. in diameter. They may be present in large numbers in persons past middle life. Their sites of predilection are the face and the upper trunk.

Histopathology. Senile hemangiomas, within a circumscribed area of the upper dermis, show numerous dilated capillaries lined by a single layer of endothelium. The epidermis shows flattening of the rete ridges (Beek). Occasionally, however, they may show acanthosis as well as hyperkeratosis and even inclusion of dilated capillaries into the epidermis. In that case, histologic distinction from angiokeratoma may be impossible (Traub and Tolmach).

NEVUS ARANEUS

Nevus araneus, or spider nevus, is characterized by a central, slightly elevated red dot from which fine blood vessels radiate. Occasionally, pulsation can be observed. Spider nevi are common on the upper half of the face.

Histopathology. According to Walsh and Becker, nevus araneus represents a small, arteriovenous anastomosis. They concluded, from serial sections, that in this lesion an arteriole ascends high into the dermis where it changes directly into a vein. The vein divides into a network of smaller venules. The latter give the lesion its spiderlike appearance, clinically.

However, it appears that nevi aranei may differ in their composition. Patek, Post and Victor found two types of vascular arrangements. In one type, they found the central vessel of the "spider nevus" to be an artery which branched successively into arterioles and capillaries. In the other type, the so-called glomus type, they found the afferent artery to be connected with the central vessel of the "spider nevus" by a short junction which had the histologic appearance of the Sucquet-Hoyer canal as seen in the cutaneous glomus. In contrast with the usual glomus, however, the central vessel of the "spider nevus" was not a collecting vein but continued into capillaries.

OSLER'S DISEASE (FAMILIAL HEMORRHAGIC TELANGIECTASIA)

This familial disease is characterized by the presence of numerous telangiectases on the skin and the mucous membranes. The presence of telangiectases on the mucous membranes may result in hemorrhages from the nose, the mouth, the stomach, the kidney, the rectum or the vagina.

Histopathology. Scattered, greatly dilated capillaries are present in the upper dermis. Fingerland and Janousek noted that the venules in the lower dermis showed narrowing of their lumina and an increase in the number of adventitial cells.

LYMPHANGIOMA

A superficial and a deep variety of lymphangioma exist. The superficial variety, lymphangioma circumscriptum, is characterized by the presence of groups of small, thick-walled vesicles resembling frog's spawn. Some of the vesicles may show a verrucous surface.

The deep variety, lymphangioma cavernosum, causes diffuse en-

largement of the affected region, for instance, macrocheilia and macroglossia.

Histopathology. In lymphangioma circumscriptum, one observes in the uppermost portion of the dermis cystically dilated lymph vessels lined by a single layer of endothelium (Fig. 230). They contain

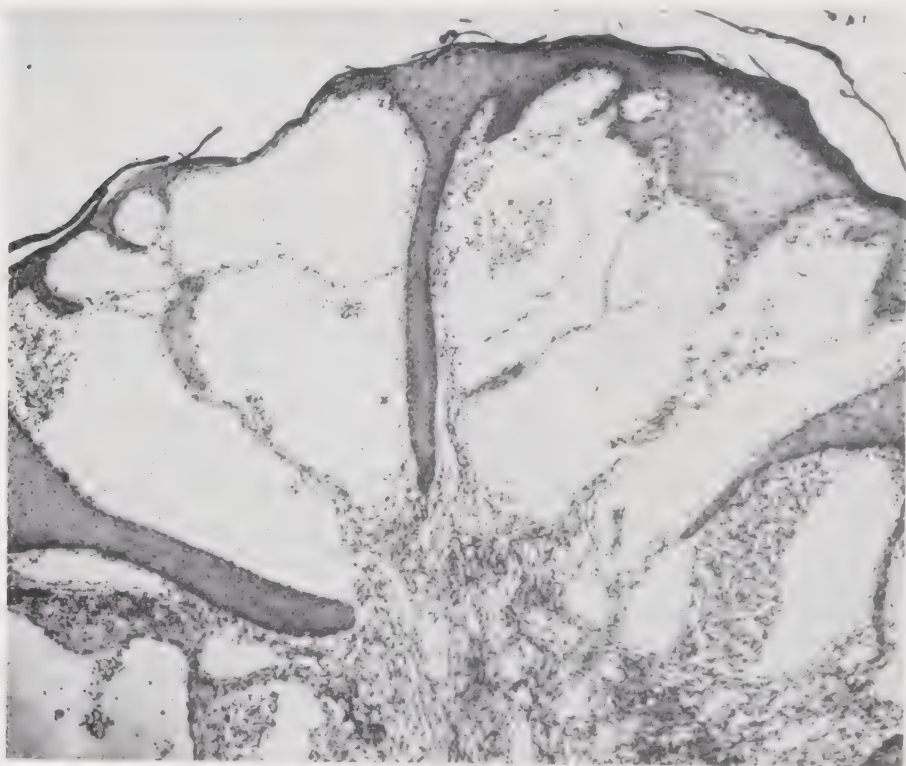


FIG. 230. **Lymphangioma circumscriptum.** Cystically dilated lymph vessels lined by a single layer of endothelial cells are present in the upper dermis. The epidermis shows downward growth and more or less surrounds some of the lymph vessels. There is moderate hyperkeratosis. ($\times 50$)

coagulated lymph and lymphocytes. The stratum malpighii varies greatly in thickness. Over some of the lymph cysts, it is thinned; elsewhere, it may show considerable acanthosis and irregular downward growth. Some of the dilated lymph vessels may be completely surrounded by epidermis. Hyperkeratosis is common. The histologic picture may be similar to that of angiokeratoma, except that the dilated areas contain lymph fluid instead of blood.

In lymphangioma cavernosum, large lymph-filled cystic spaces lined by a single layer of endothelium are present in the dermis and the subcutaneous tissue. There is concomitant hypertrophy of the connective tissue.

GLOMUS TUMOR

This tumor usually occurs as a single, small, deep-seated, pink or purplish nodule, which is tender and gives rise to severe paroxysmal pains. In rare instances, there are numerous lesions in which case tenderness is absent in most of them (Weidman and Wise; Eyster and Montgomery). The most common sites of the solitary lesions are

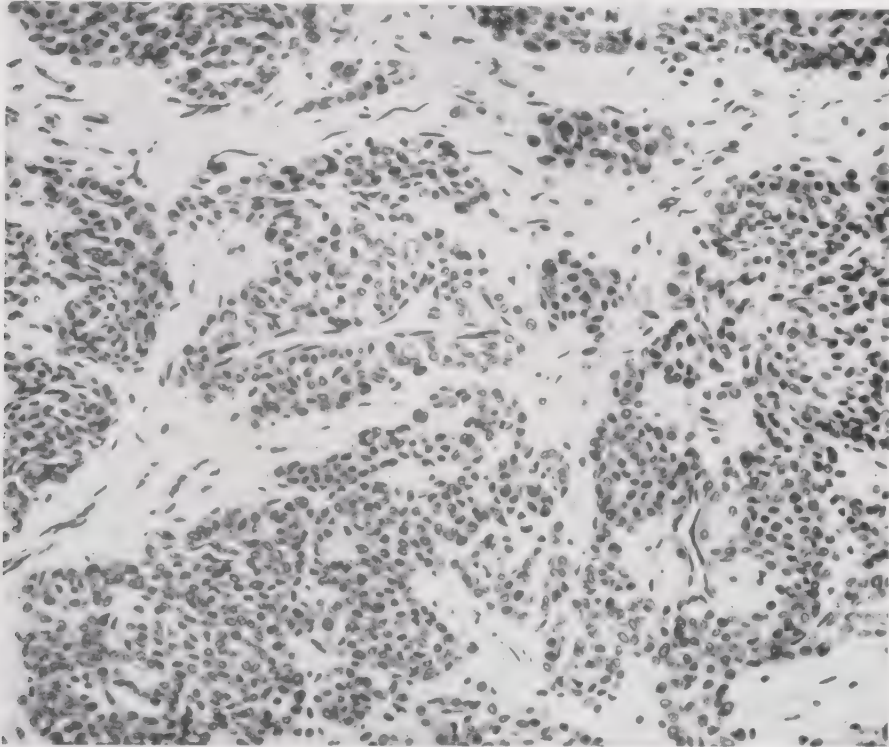


FIG. 231. Glomus tumor. There are numerous vascular lumina of varying size lined by a single layer of endothelial cells and surrounded by proliferating rows of glomus cells. However, some of the masses of glomus cells do not show a central vessel. ($\times 200$)

the nail bed and the fingertips; however, the lesions may occur elsewhere.

Histopathology. The glomus tumor represents a benign tumor of the cutaneous glomus, a structure composed of an arterial segment, the Sucquet-Hoyer canal and a venous segment. The normal Sucquet-Hoyer canal possesses a narrow lumen lined with a single layer of endothelial cells and a thick mantle of glomus cells (see page 24). Glomus cells have a faintly eosinophilic cytoplasm and large, oval, pale nuclei with a distinct chromatin structure. Thus, they resemble epithelioid cells. They are richly supplied with nonmyelinated nerve fibrils.

A glomus tumor is composed of vascular lumina and numerous

glomus cells. As a rule, the lumina are small, but sometimes, especially in those cases with multiple lesions, the lumina are of considerable size (Weidman and Wise; Eyster and Montgomery). The vascular lumina are lined by a single layer of flattened endothelial cells and, usually, by several layers of glomus cells (Fig. 231). Some of the vessels closely resemble the Sucquet-Hoyer canals of the normal glomus. In many areas, the glomus cells proliferate irregularly from the vascular walls into the connective-tissue stroma of the tumor. In addition, masses of glomus cells without central lumina and scattered glomus cells are present in the stroma.

The connective-tissue stroma of the tumor is loose, edematous and contains scattered fibroblasts and glomus cells. It may show marked mucoid degeneration. Special staining for nerve fibers (Bodian stain) will reveal numerous nerve fibers, most of them nonmyelinated. They show considerable branching and terminate as fine fibrils around the glomus cells.

HEMANGIOPERICYTOMA

This rare tumor may arise wherever there are capillaries. Its most common sites are the skin and the subcutaneous tissue. Hemangio-

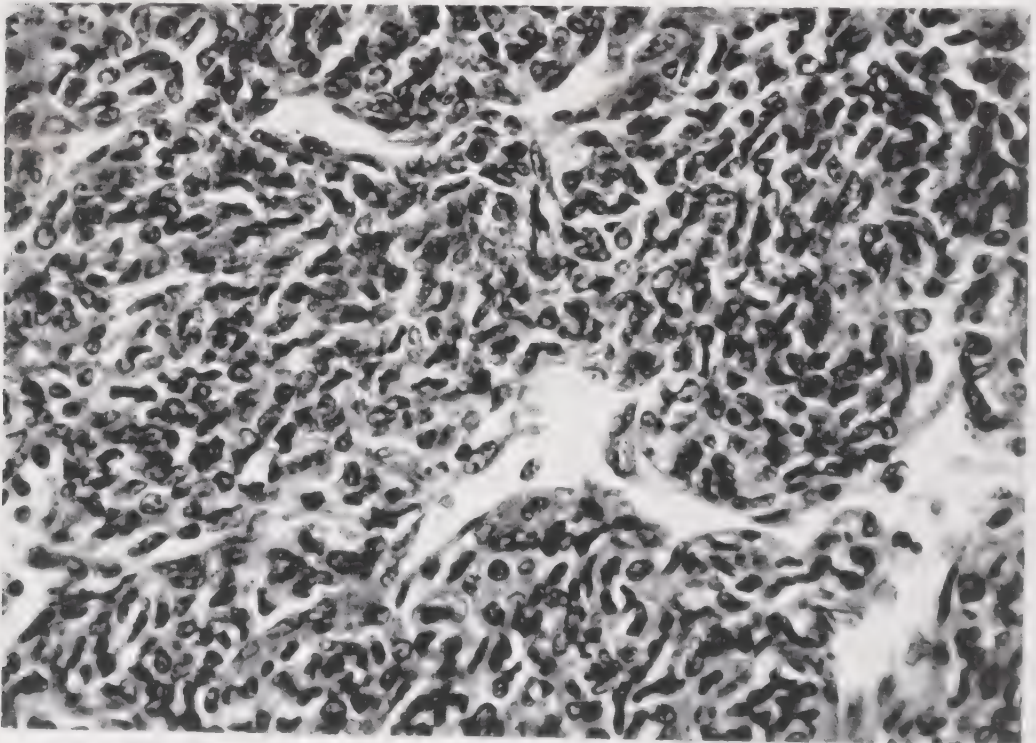


FIG. 232. Hemangiopericytoma. The capillary lumina are lined with a single layer of endothelial cells and are surrounded by irregularly proliferating, closely packed pericytes. Most of the pericytes are spindle shaped. ($\times 400$)

pericytomas have no diagnostic clinical appearance. They are of varying size, firm and nodular. Some are benign, some are gradually growing and some even metastasize.

Histopathology. The tumor is characterized by the presence of endothelial tubes and sprouts surrounded by irregularly proliferating, closely packed cells which are oval or spindle-shaped (Fig. 232) (Stout; Sims, Kirsch and MacDonald). These proliferating cells are pericytes, a contractile cell first described by Zimmermann (see page 24). Occasionally, the capillaries are difficult to locate, in which case a reticulum stain will aid in making them more easily recognizable.

In some cases, the pericytes show frequent mitotic figures and invasion into vascular lumina so that the tumor must be regarded as malignant or, at least, potentially malignant (Fisher, Kaufman and Mason). In one instance, widespread metastases, resulting in death, have been reported (Forrester and Houston).

Differential Diagnosis. Hemangiopericytoma somewhat resembles a glomus tumor, which is easily understood since the glomus cell represents a modified pericyte and the cells in the glomus tumor are arranged in a manner similar to that of hemangiopericytoma: outside of capillary lumens lined by a thin endothelium. However, the cells in the glomus tumor show a more orderly arrangement and are more uniform in appearance, being round to oval and never spindle-shaped.

KAPOSI'S SARCOMA (MULTIPLE IDIOPATHIC HEMORRHAGIC SARCOMA)

Kaposi's sarcoma consists of an eruption of multiple bluish red or dark-brown nodules and plaques. The lesions not infrequently show a verrucous surface. They may undergo ulceration. Spontaneous involution of some of the lesions occurs occasionally. The sites of predilection are the distal portions of the extremities, but other areas of the skin may also become involved.

Visceral lesions occur in about 10 per cent of the cases (Tedeschi, Folsom and Carnicelli). The most frequent sites are, in order of frequency, the gastro-intestinal tract, the liver, the lungs and the retro-peritoneal and the mesenteric lymph nodes (Dörffel). In rare instances, there may be visceral lesions of Kaposi's sarcoma without cutaneous involvement (Tedeschi, Folsom and Carnicelli).

Histogenesis. The histogenesis of Kaposi's sarcoma is not fully ascertained. A widely accepted view (with which the author agrees) is that Kaposi's sarcoma is a benign angiomatosis arising from embryonal vascular cells and that the lesions are autochthonous in origin rather than metastatic (Gilchrist and Ketron; Lang and Hasl-

hofer; Becker and Thatcher; Tedeschi, Folsom and Carnicelli). Dissenting views are held by Pautrier and Diss, who regard Kaposi's sarcoma as a neurovascular dysgenesis, and by Dörffel, who regards it as a disease of the reticulo-endothelial system and related to the lymphoma group of diseases. The idea that the disease is a sarcoma, proposed originally by Kaposi, has been abandoned by most writers.

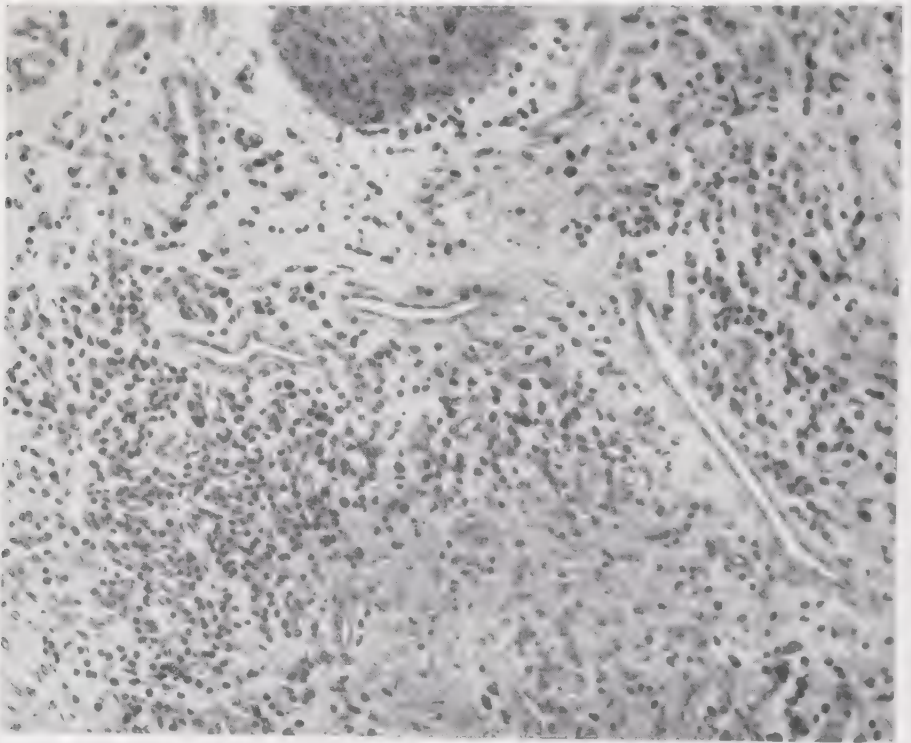


Fig. 233. Kaposi's sarcoma, early granulomatous stage. The capillaries are increased in size and number. Their endothelial cells are large. A diffuse, chronic inflammatory infiltrate is present. In the lower central section of the illustration, one can see groups of endothelial cells attempting to form new blood vessels. ($\times 200$)

Nevertheless, some authors (Aegerter and Peale; Sachs, Azulay and Convit) still maintain that it represents a sarcoma.

Evidence against the concept of Kaposi's sarcoma as sarcoma and in favor of the autochthonous rather than the metastatic origin of the lesions are (1) the absence of a primary focus that progressively enlarges, (2) the appearance of widely separated lesions in crops, (3) the spontaneous regression of some lesions and (4) the fact that histologic examination may reveal very early stages of development in late-appearing lesions. Occasionally, however, a lesion may undergo malignant degeneration and then grow as a true sarcoma and cause metastases.

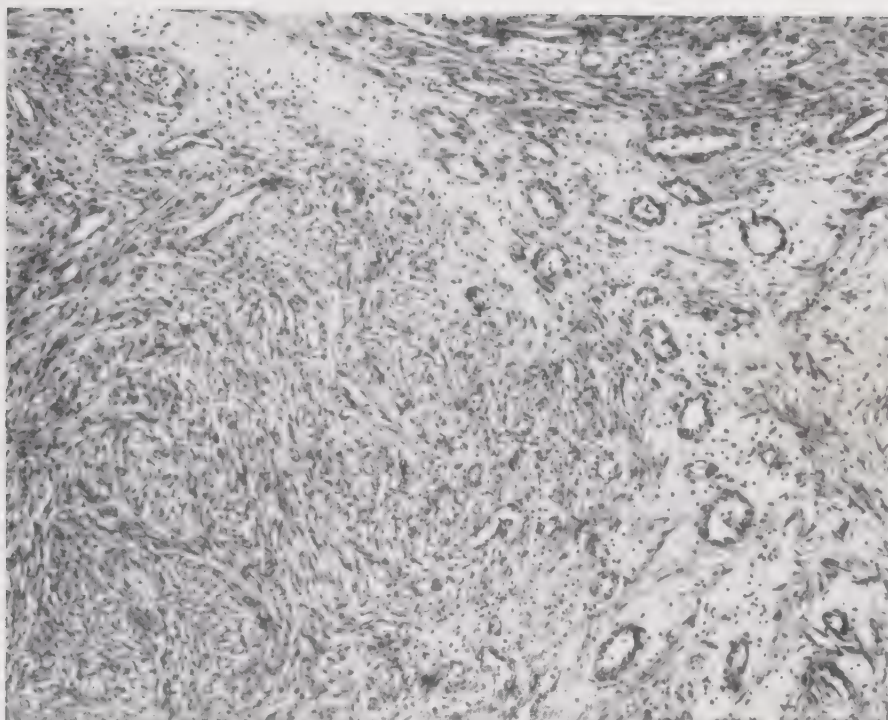


FIG. 234. Kaposi's sarcoma, neoplastic stage. On the left, the neoplasia is fibroblastic; on the right, it is angiomatous. ($\times 100$)

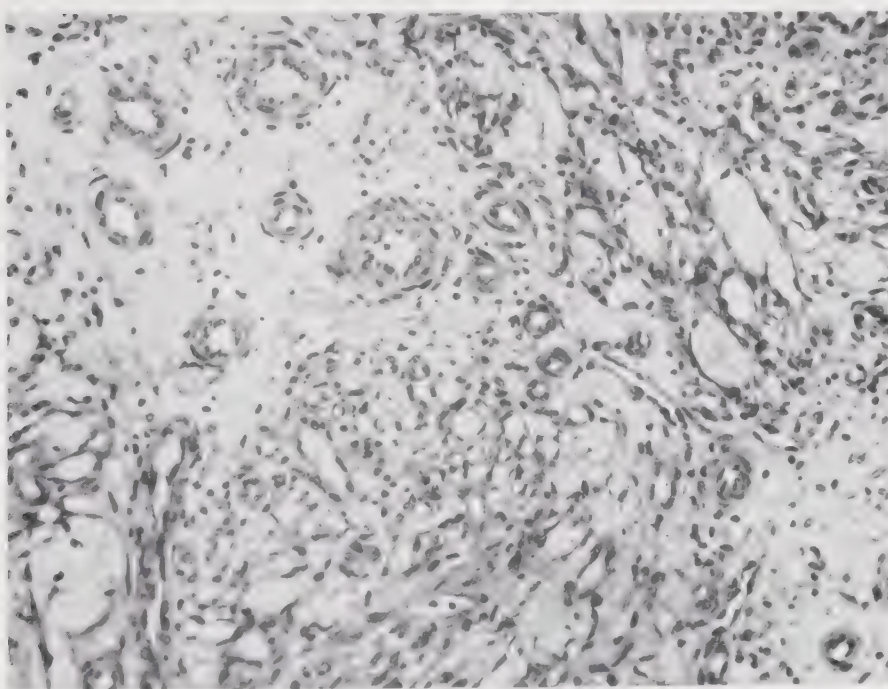


FIG. 235. Kaposi's sarcoma, angiomatous lesion. There are numerous vascular lumina. Most lumina are lined by only a single layer of endothelial cells, but some are surrounded also by perithelial cells. The stroma is edematous and contains extravasated erythrocytes. ($\times 200$)

Histopathology. The two types of cells of which capillaries are composed participate in the formation of the lesions: endothelial and perithelial cells. The perithelial cell is a pericapillary histiocyte which may develop into a fibroblast (see page 33). In addition, an inflammatory reaction is observed in early lesions. One may divide the lesions of Kaposi's sarcoma into early granulomatous lesions and late neoplastic lesions. The latter may be either "angiomatous," if endothelial-cell proliferation predominates, or "fibroblastic," if perithelial-cell proliferation predominates.

In early granulomatous lesions, the blood vessels of the dermis are dilated and increased in number (Fig. 233). Their endothelial cells are swollen. There is perivascular as well as diffuse cellular infiltration, varying in severity. The infiltrate is composed of lymphocytes, plasma cells and some histiocytes and fibroblasts. One may see groups of endothelial cells attempting to form new blood vessels. Frequently, one sees small groups of extravasated erythrocytes and deposits of hemosiderin. The histologic picture in the early stage is not always diagnostic; however, the presence of extravasated erythrocytes and of hemosiderin in a granulomatous lesion as described above should always make one think of early Kaposi's sarcoma.

In late lesions, the histologic picture may be either angiomatous or fibroblastic; frequently, both phases are found intermingled in the same lesion (Fig. 234). In angiomatous lesions one finds numerous vascular lumina. They vary greatly in size and occasionally are saccular. Most lumina show only a single layer of swollen endothelial cells, but some are surrounded, in addition, by perithelial cells (Fig. 235). The stroma in which the vessels are embedded often is edematous and usually contains hemorrhages and hemosiderin deposits.

In fibroblastic lesions, one observes marked proliferation of spindle-shaped cells which represent young fibroblasts (Symmers) and are derived from perithelial cells. They lie in strands which extend irregularly in all directions. The nuclei vary in size and staining qualities and some of them are atypical. Mitotic figures are present, though usually in small number. The histologic picture is thus very much like that of a fibrosarcoma. One feature, however, distinguishes the fibroblastic lesions of Kaposi's sarcoma from fibrosarcoma and that is the presence of small or large groups of extravasated erythrocytes and of granules of hemosiderin between the fibroblasts. This feature sometimes is not conspicuous, but a thorough search or staining for iron almost invariably will reveal such areas (see Plate 3). The fibroblasts, being immature, form only little collagen, as a rule, but staining with Foot's stain will reveal a rather dense network of reticulum fibers produced by them (Symmers). (As discussed on page

20, reticulum represents young collagen.) In old, regressing lesions, one may find considerable collagenization due to maturation of the young fibroblasts. This may lead eventually to fibrosis, cicatrization and disappearance of the lesion.

If malignant degeneration occurs in a lesion of Kaposi's sarcoma, the resulting sarcoma is indistinguishable from fibrosarcoma.

Seven instances are recorded in the literature in which lymphoma occurred in patients with Kaposi's sarcoma. In four of these patients, lymphocytic lymphoma was present (Cole and Crump; Hufnagel and Dupont; Sachs and Gray; Fischer and Cohen), in two mycosis fungoides (Lane and Greenwood; Winer), and in one Hodgkin's disease (Greenstein and Consten). There is not sufficient proof that Kaposi's sarcoma and lymphoma are related. It is, therefore, best to regard their coexistence as accidental.

HEMANGIO-ENDOTHELIOMA (HEMANGIOSARCOMA)

Malignant tumors arising from blood vessels are rare. According to the two types of cells of which capillaries are composed, perithelial cells and endothelial cells, two types occur: hemangio-fibrosarcoma and hemangio-endothelioma.

Hemangio-fibrosarcomas have the histologic appearance of fibrosarcomas with conspicuous capillary proliferation and may, therefore, be regarded as fibrosarcomas. The sarcomas which occasionally arise in lesions of Kaposi's sarcoma are of that type. This leaves hemangio-endothelioma as the only specific malignant tumor arising from blood vessels.

Hemangio-endothelioma usually occurs as a diffusely infiltrating mass which is soft, dark-red and raised above the surface of the skin. It grows slowly but progressively and may attain large size. Metastases occur relatively late (Caro and Stubenrauch).

Histopathology. Hemangio-endothelioma is characterized (1) by the presence of atypical endothelial cells in greater numbers than required to line the vessels with a simple endothelial membrane and (2) by the new formation of vascular tubes with a marked tendency for their lumina to anastomose (Stout).

The number of vascular lumina varies in different tumors, but, as a rule, vascular lumina are numerous. They are irregular in size and shape. Large, tortuous sinuses may be present (Fig. 236). The vascular channels are lined by large, atypical endothelial cells. In many areas, endothelial cells lie in several layers and proliferate into the lumina to such a degree that the vascular tubes are completely obscured and cannot be made out as such when routine stains are used. When, however, a reticulum stain is used, the outline of the vessels

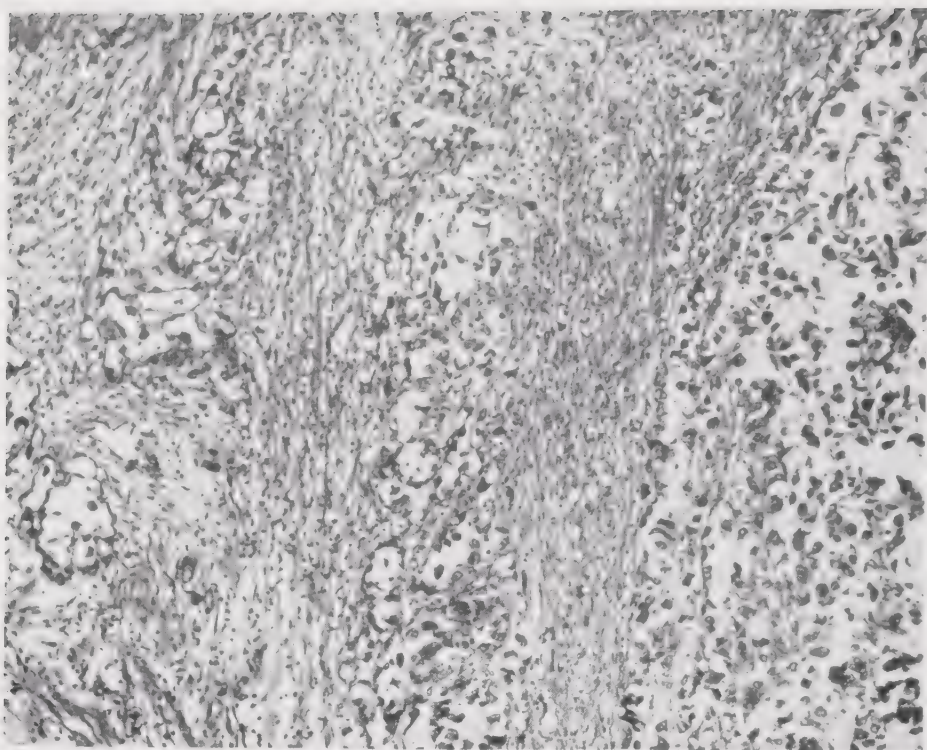


FIG. 236. Hemangio-endothelioma. Low magnification. There are numerous vascular lumina; on the right side is a large vascular sinus. The vascular channels are lined by large, atypical endothelial cells which in some areas proliferate irregularly into the lumina. ($\times 100$)

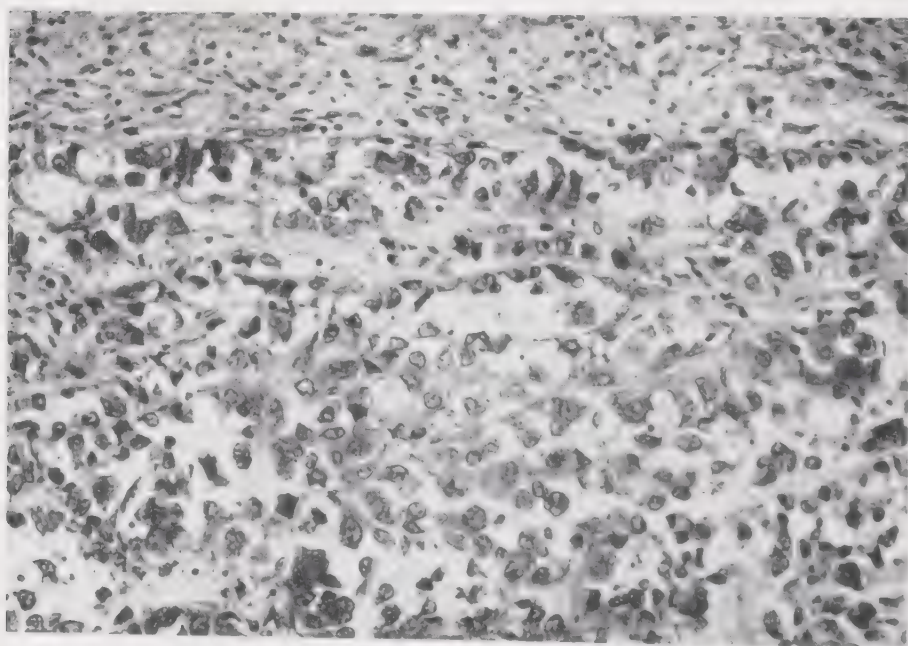


FIG. 237. Hemangio-endothelioma. High magnification of Figure 236. A large sinus is shown into which atypical endothelial cells proliferate. Some of the endothelial cells are multinucleated. ($\times 200$)

can be seen. In some tumors, one may see endothelial cells extend as invading cords between the fibers of the connective tissue and, occasionally, they may occur in large, solid sheets.

The endothelial cells seen in this tumor are large and polyhedral and have a well-defined cellular membrane and relatively clear cytoplasm (Fig. 237). The nuclei tend to be round to oval, pale and vesicular. However, many nuclei are atypical, being irregular in shape and hyperchromatic. In addition, numerous mitotic figures are usually present. Some of the endothelial cells are multinucleated.

POST-MASTECTOMY LYMPHANGIO-SARCOMA

Lymphangio-sarcoma may occur in post-mastectomy lymphedema (Stewart and Treves). Several years after radical mastectomy for carcinoma, subcutaneous and cutaneous nodules appear in the edematous tissue of the arm on the side of the operation. The cutaneous nodules have a bluish color. The clinical resemblance to Kaposi's sarcoma may be great. The nodules are not radio-sensitive. Metastases, especially to the lungs, occur.

Histopathology. The nodules are composed of large, atypical cells which, in some places, form solid proliferations and, in others, produce capillary vessels and lacunar structures. The lumens are usually empty, but, in some cases, contain occasional accumulations of red blood cells. In such cases, the tumor represents a mixed lymphangio- and hemangio-endothelioma (Jessner, Zak and Rein). Outside the tumor formations, one observes numerous dilated, proliferating lymphatics in the dermis, in the subcutaneous tissue and even deeper, in the intermuscular fascia.

Differential Diagnosis. The resemblance to hemangio-endothelioma is so great that differentiation is impossible except perhaps on the basis of the amount of red blood cells in the lumina. The tumor differs from Kaposi's sarcoma by the intralymphatic proliferation and greater atypicality of the endothelial cells and by the absence of atypical fibroblastic formations.

6. TUMORS OF MUSCULAR TISSUE

LEIOMYOMA

There are three types of leiomyoma of the skin: (1) multiple cutaneous leiomyomas, (2) solitary angioleiomyomas and (3) solitary genital leiomyomas (myomes dartoïques).

Multiple cutaneous leiomyomas are from pinhead- to pea-sized, brown or bluish, firm, elevated nodules which tend to occur either

on the back, the face or the extensor surfaces of the extremities and usually are arranged in groups. They often are painful and sensitive to pressure.



FIG. 238. **Leiomyoma, nonvascular type.** The tumor is composed of interlacing bundles of smooth-muscle fibers. The nuclei of the smooth-muscle fibers are thin, long and blunt-edged. Collagen bundles are intermingled with the smooth-muscle bundles. Both stain alike with hematoxylin-eosin. To differentiate them, an aniline blue stain may be used. (See Plate 4.) ($\times 100$)

Solitary angioleiomyomas usually are subcutaneous in location but are adherent to the overlying skin. They rarely grow larger than 1 cm. in diameter and usually are nontender.

Solitary genital leiomyomas are located either on the scrotum, the labia majora or, rarely, on the nipples. They may attain considerable size, several centimeters in diameter, and are nontender.

Histopathology. Multiple cutaneous leiomyomas arise from the arrectores pilorum muscles, solitary angioleiomyomas from the smooth

muscle of veins, and genital leiomyomas from either the muscularis sexualis or the muscularis mamillae (Stout).

All leiomyomas are composed of interlacing bundles of smooth muscle fibers (Fig. 238). Proliferating collagen bundles are often intermingled with the smooth muscle bundles. The muscle fibers composing the bundles are straight or slightly wavy and contain centrally located, thin, very long, blunt-edged nuclei. The muscle bun-



FIG. 239. **Angioleiomyoma.** A large vein with a thick muscular wall is present within a leiomyoma. The muscle bundles of the vein merge with those of the tumor. ($\times 200$)

dles stain pink with hematoxylin-eosin just as collagen does and often are difficult to distinguish from it. In order to differentiate muscle from collagen, an aniline blue stain may be used. With this stain, muscle stains red and collagen blue (see Plate 4).

Multiple cutaneous leiomyomas are located in the dermis, are not encapsulated and contain only few blood vessels.

Solitary angioleiomyomas lie largely in the subcutaneous tissue, are encapsulated and contain large blood vessels, probably veins, with thick muscular walls (Fig. 239). Some of these vessels have a stellate lumen because of contraction of the muscular tissue. In some areas, one sees the muscle bundles of the vessels merge with those of the tumor (Jansen).

Solitary genital leiomyomas are located largely in the subcutis, are not encapsulated and contain only a few small blood vessels but often a rather large amount of collagen.

GRANULAR-CELL MYOBLASTOMA

Granular-cell myoblastomas are solitary tumors occurring most commonly in the tongue, the skin and the subcutaneous tissue (Crane and Tremblay). They usually are benign, but malignant degeneration occurs occasionally (Ross, Miller and Foote). Cutaneous myoblastomas usually consist of a firm, round, well-circumscribed, non-

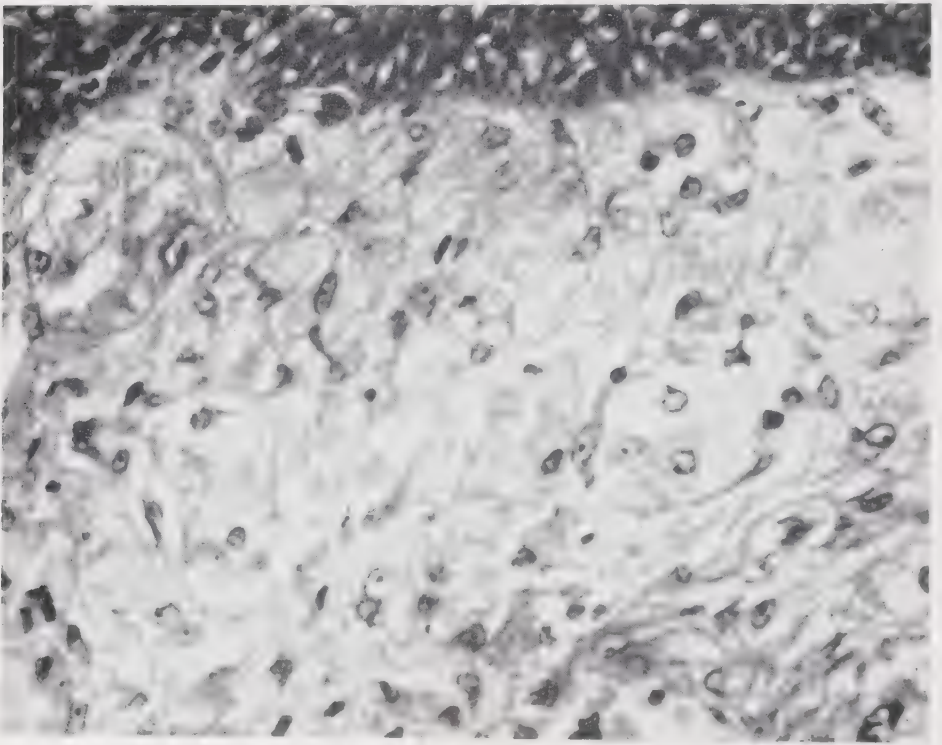


FIG. 240. Granular-cell myoblastoma. The tumor is composed of large cells having a pale cytoplasm filled with coarse granules. ($\times 400$)

tender nodule, from 0.5 to 2 cm. in diameter, which may lie within the thickness of the skin or may be pedunculated. In some instances, the surface of the tumor is hyperkeratotic. Subcutaneous myoblastomas consist of a firm nodule which may or may not be attached to the overlying skin.

Histopathology. On histologic examination, the cells of the tumor appear large and polyhedral. Most cells measure from 20 to 60 microns in diameter, but some are even larger. They have a pale cytoplasm filled with coarse acidophilic granules (Fig. 240). The nuclei are small, round or oval and somewhat vesicular (Cipollaro and Einhorn). Some cells contain more than one nucleus. Delicate strands of collagen surround the cells of the tumor.

The overlying epidermis usually is hyperplastic and, not infre-

quently, shows active downward proliferation, even with horn-pearl formation (Fig. 241) (Bloom and Ginzler). This pseudo-epitheliomatous hyperplasia has been mistaken for squamous-cell carcinoma in several cases reported in the literature (Eickhoff).

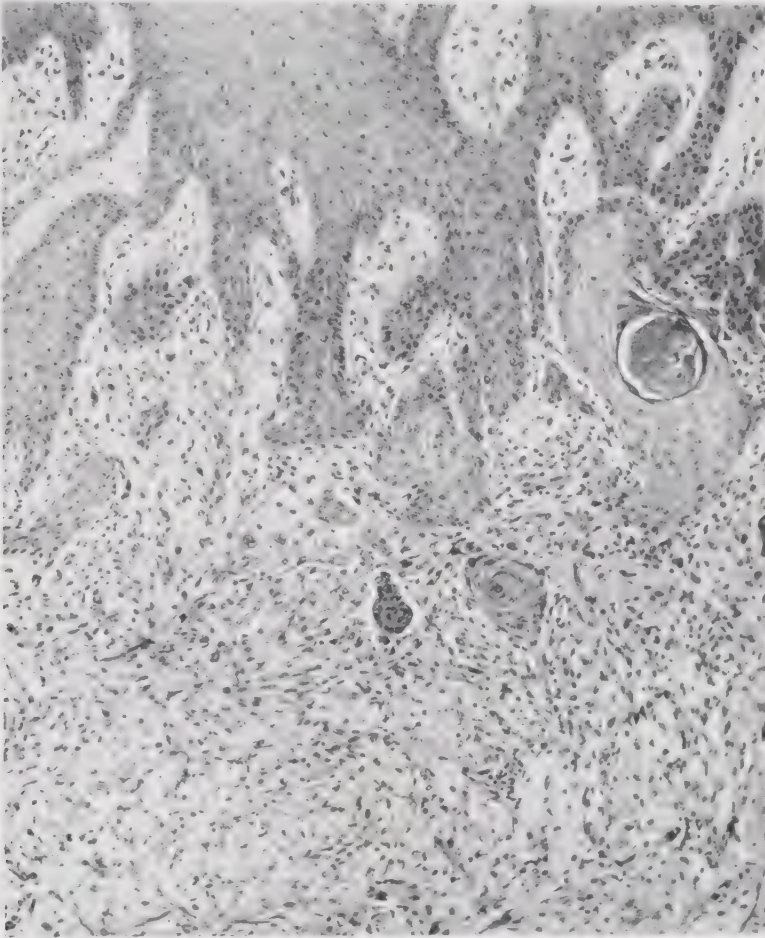


FIG. 241. Granular-cell myoblastoma. The epidermis shows pseudo-epitheliomatous hyperplasia. The dermis contains numerous large, pale cells as they are typical of this tumor. ($\times 200$)

In lesions of the tongue, one not infrequently sees areas suggesting transitions between the tumor cells and mature muscle fibers (Crane and Tremblay). This observation has been the reason that granular-cell myoblastomas were at first generally regarded as tumors of immature striated muscle cells (myoblasts). However, in recent years, several authors have expressed the view that these transitions were only apparent and that granular-cell myoblastomas were composed of either schwannian cells or endoneural fibroblasts and thus were of neural origin (Fust and Custer; Ashburn and Rodger; Bangle).

The reasons these authors have given are: first, granular cells occasionally are arranged concentrically around a core consisting of bundles of axis cylinders (Fust and Custer); second, groups of granular cells have been found within nerve sheaths both within and in the vicinity of the tumor (Fust and Custer; Ashburn and Rodger) and, third, the granules stain slightly positive for lipids, suggesting that they form as a result of the disintegration of axis cylinders and myelin sheaths (Bangle).

In the rare cases of malignant granular-cell myoblastomas, one can observe all stages of transition from typical granular cells to malignant spindle and giant cells devoid of granules. Widespread hematogenous metastases may occur (Ross, Miller and Foote).

Differential Diagnosis. On cursory examination, the large, pale cells of the tumor resemble the foam cells of xanthoma. However, the cells of granular-cell myoblastoma contain a granular and not a foamy cytoplasm and take fat stains only very faintly. Furthermore, in granular-cell myoblastoma, the overlying epidermis tends to be hyperplastic rather than atrophic as in xanthoma.

7. TUMORS OF OSSEOUS TISSUE

OSTEOMA CUTIS

Cutaneous bone formation may be primary (heterotopic) or secondary (metaplastic). Only lesions with primary bone formation should be called osteomas.

In primary bone formation, bone develops in areas which were not the site of previous lesions. The bone probably develops from embryonal rests. Such lesions therefore represent nevoid tumors or hamartomas (Hopkins; Dietrich; Vero, Machacek and Bartlett).

In secondary bone formation, bone develops in areas of tissue degeneration. Bone may develop in tumors, particularly in the calcifying epithelioma of Malherbe (see page 368), in scar tissue (Lilga and Burns), in lesions of scleroderma, in various granulomas and in areas of fat necrosis or hemorrhage. Also, multiple small foci of ossification may occur in the skin of the face in prolonged, severe acne with scarring (Leider). In all these instances, the bone develops by metaplasia and frequently, though not always, calcification precedes the ossification.

Osteomas may be single (Dietrich) or multiple (Hopkins; Vero, Machacek and Bartlett; Tijdens and Ruiter). Their clinical appearance is not uniform. Usually, they occur as small, hard plaques or nodules within the dermis or subcutis.



FIG. 242. Osteoma cutis. Low magnification. The bone appears lamellated about several Haversian canals. ($\times 100$)

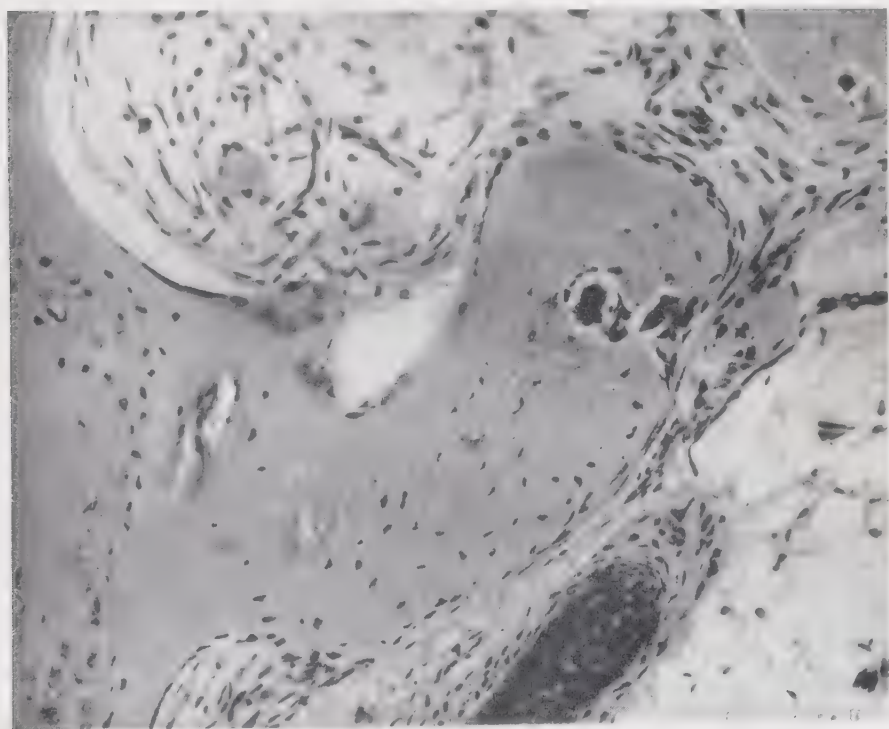


FIG. 243. Osteoma cutis. High magnification of Figure 242. The bone is lined in many areas by osteoblasts. In the center of the field, several osteoclasts lie within a niche, called Howship's lacuna. ($\times 200$)

Histopathology. On histologic examination, one or several pieces of bone are observed within a lesion. The bone appears lamellated in concentric rings about several Haversian canals. These canals contain blood vessels and connective tissue (Fig. 242). Most of the bone lamellae contain numerous small lacunae, each filled with a cell. These cells, called osteocytes, possess various shapes; some of them are stellate. Along the margin of the bone one sees many osteoblasts which build bone and a few osteoclasts which absorb bone. The osteoblasts have small, oval or elongated nuclei. As they lay down bone substance, they become enclosed in the bone as osteocytes. The osteoclasts have multiple large nuclei and resemble multinucleated foreign-body giant cells. Frequently, they lie within deep grooves, called Howship's lacunae, which extend into the bone substance (Fig. 243).

The tissue surrounding the piece or pieces of bone often is highly vascular and cellular and may contain fat cells, so that it resembles bone marrow.

Occasionally, one may find in osteomas not only bone but also fibrocartilage (Vero, Machacek and Bartlett).

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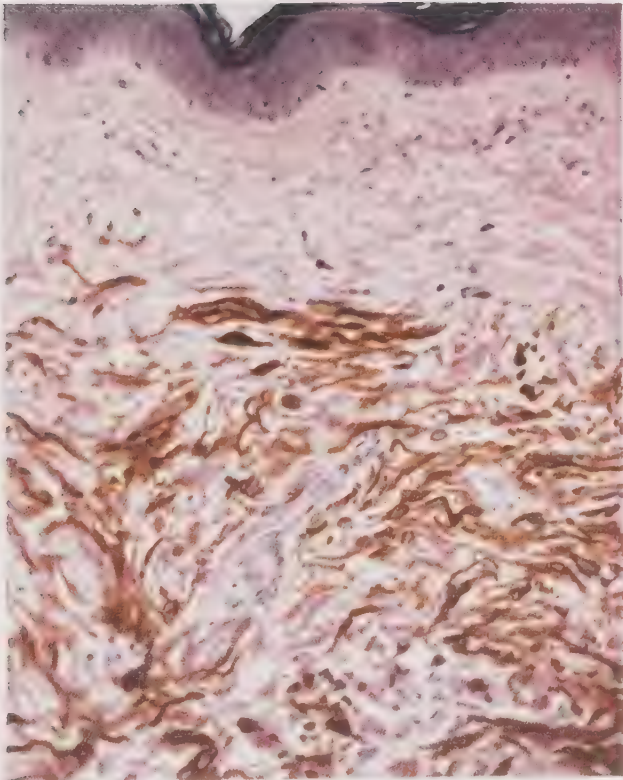
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PLATE 4

Leiomyoma. Aniline blue (Mallory) stain. This stain serves to differentiate collagen from smooth muscle. With hematoxylin-eosin both stain red, but with aniline blue collagen stains blue and muscle red. ($\times 175$)



Blue nevus. Numerous large, spindle-shaped, deeply pigmented cells are located in the lower dermis. They are melanoblasts. ($\times 175$)

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20

Pigmented Nevi and Malignant Melanoma

Pigmented nevi and malignant melanomas are composed of nevus cells. Lentigo, the Mongolian spot, and the blue nevus represent special types of pigmented nevi which will be discussed at the end of this chapter.

PIGMENTED NEVUS

From a histologic point of view, it is practical to divide pigmented nevi into intradermal (resting) nevi and junction (active) nevi. However, intermediary forms, so-called compound nevi, are common. It is thus understandable that one cannot always predict from the clinical appearance whether a nevus is of the intradermal type or the junction type.

The intradermal nevus, as a rule, is a circumscribed, smooth or slightly verrucous elevation which may or may not contain a number of hairs and varies in color from normal skin to dark brown. Intradermal nevi are very rare on the palms, the soles and the genitalia. Nevi located in these locations almost always are junction nevi.

The junction nevus is a relatively flat or slightly raised, smooth, pigmented mark that is devoid of hairs. Its color is light brown or brownish black, rarely slate-blue or bluish black. The majority of the marks that are slate-blue or bluish black are not junction nevi but blue nevi.

Histogenesis of the Nevus Cell. In former years, the nevus cell had been thought to be of epidermal origin. Unna believed that nevus cells were modified basal cells that had migrated ("dropped off") from the epidermis into the dermis ("Abtropfung" theory). Today, there are but few adherents of this theory (Allen). The great majority of investigators have accepted the theory, first proposed by Masson in 1926, that both the melanocytes in the epidermis, the so-called clear cells, and the nevus cells are of neural origin (see page 5). Masson stated that nevus cells may develop from two sources: from melanocytes in the epidermis and from schwannian cells of cutaneous nerves. He believed that junction nevi develop exclusively from

melanocytes, whereas compound and intradermal nevi develop from both melanocytes and schwannian cells. So long as there was migration of melanocytes from the epidermis into the dermis, the nevus was a compound nevus, but, when this migration ceased, it became an intradermal nevus. Thus, compound and intradermal nevi, according to Masson, have a dual origin from two primordia which fused together. This dualistic view of the origin of compound and intra-

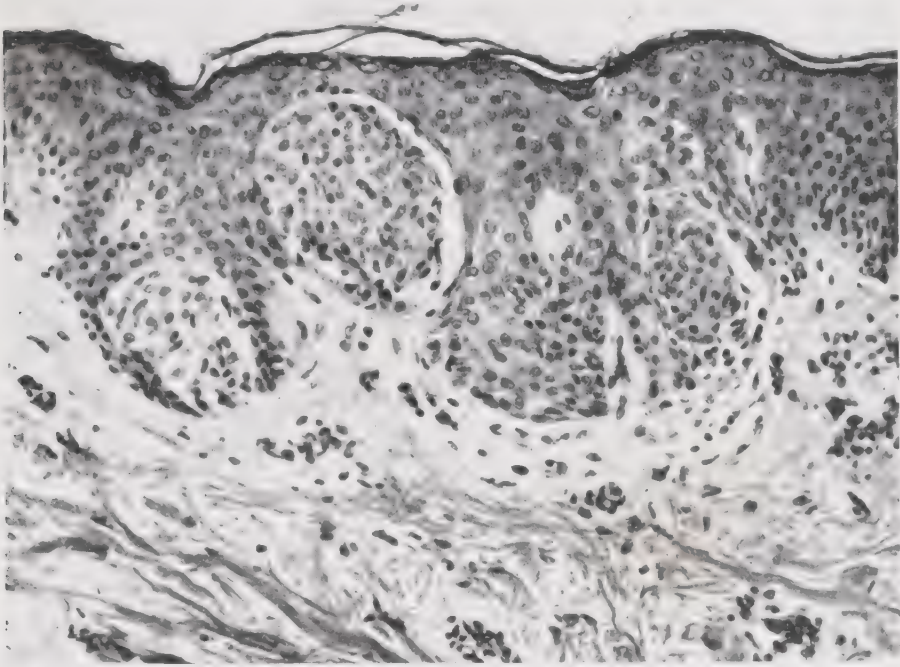


FIG. 244. Junction nevus. Well-circumscribed nevus cell nests are present in the lower epidermis. Otherwise, the epidermis appears normal. This type of junction nevus is not apt to become malignant. ($\times 200$)

dermal nevi has been questioned by some authors (Lund and Stobbe) who believe that all pigmented nevi develop solely by "dropping off" of melanocytes.

As evidence in favor of his theory of the neural origin of nevi, Masson cited his observation that in the superficial portions of nevi the nevus cells lie in nests resembling Meissner corpuscles while in the deep portions they lie in strands resembling strands of schwannian cells. He further pointed out that the strands in the deep portions frequently contain nerve-like elements ("neuroid tubes" and "lames foliacées"—see below). Additional evidence in favor of Masson's theory is the observation by Berkheiser and Rappoport that nevus cells may be found proliferating within the perineural sheath of superficial cutaneous nerves.

Histopathology. In a junction (active) nevus, there is active formation of nevus cells in the basal layer of the epidermis (i.e., at the epidermal-dermal junction) and no nevus cell nests are found in the dermis. In a compound nevus, there also is junction activity; but, in addition, well-formed nevus cell nests are present in the dermis. In an intradermal nevus junction, activity is no longer present and the

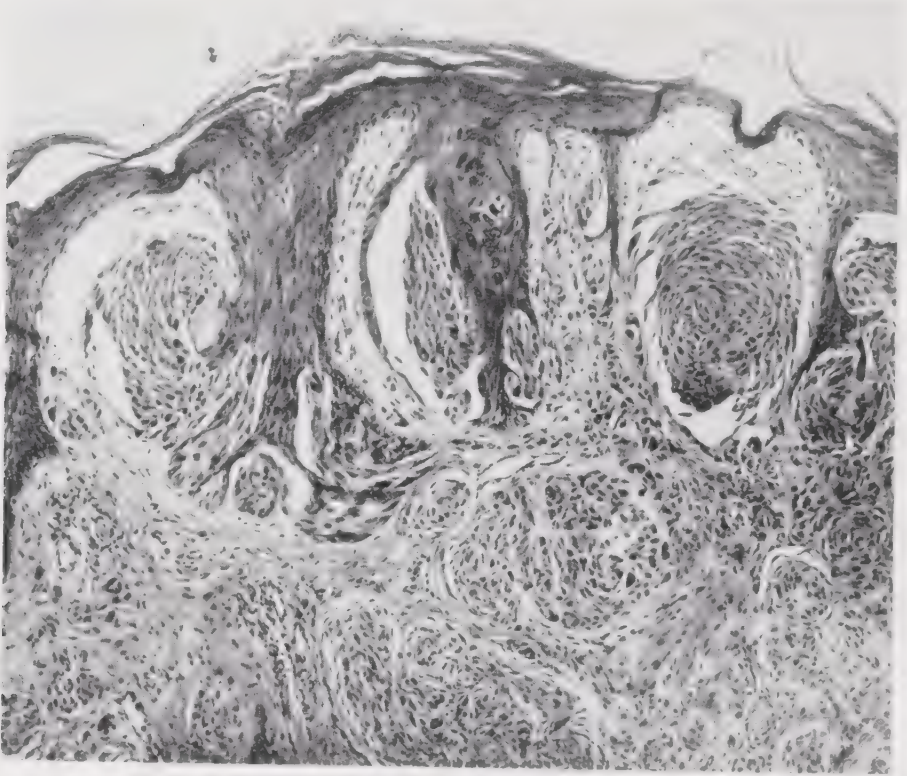


FIG. 245. Nevus pigmentosus, compound type. The cells composing the intra-epidermal and the subepidermal nevus cell nests are spindle-shaped and resemble schwannian cells. The nevus cell nests suggest Meissner tactile bodies. ($\times 100$)

nevus cells are all located in the dermis. However, completely intradermal (resting) nevi are rare: if serial sections are made it will be seen that nearly all intradermal nevi show at least a few areas of junction activity.

That the development from junction nevus into a compound nevus and, further, into an intradermal nevus is a matter of aging of a nevus is suggested by the observation of Lund and Stobbe that a much higher percentage of nevi show junctional activity in children than in adults. Only nevi located at the distal portions of the extremities were found consistently to be junction nevi, even in adults.

The typical nevus cell is oval or cuboidal in shape and has a dis-

tinctly outlined, homogeneous cytoplasm. The nucleus is large, round or oval, pale and vesicular. Nevus cells, however, show variations in appearance. In the upper dermis, they may appear like epithelial or epithelioid cells, while, in the lower dermis, they may resemble histiocytes, fibroblasts or schwannian cells.

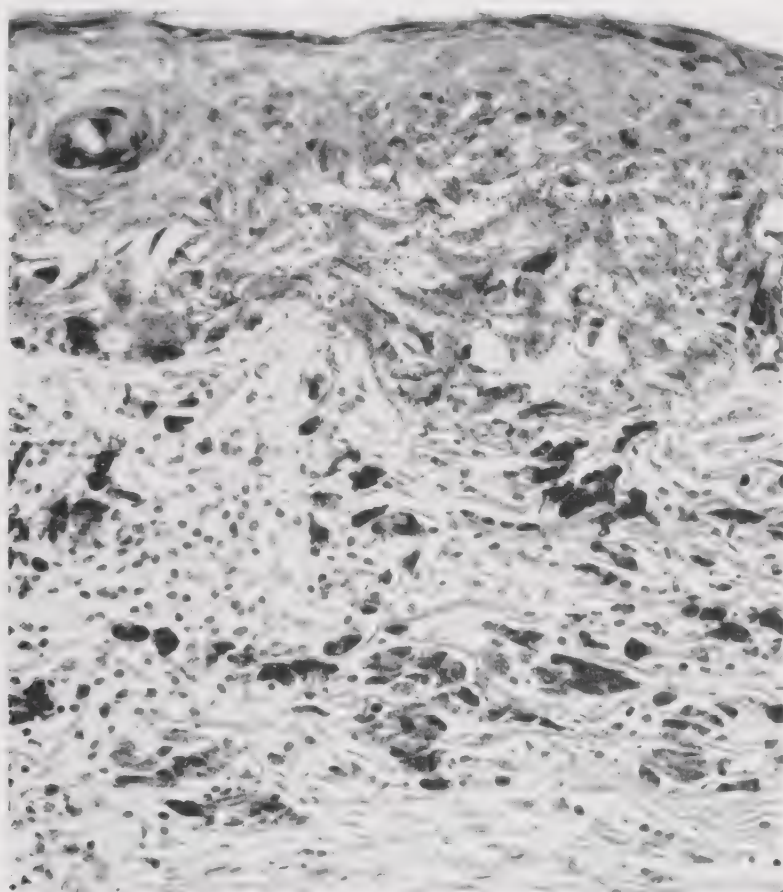


FIG. 246. **Junction nevus of the premalignant type.** Nevus cells lie diffusely scattered in the lower epidermis, which appears disorganized. No actual invasion of the nevus cells into the dermis is present, however. The upper dermis contains a bandlike inflammatory infiltrate intermingled with melanophores. (It is possible that this type of junction nevus actually represents the earliest phase of a malignant melanoma.) ($\times 200$)

JUNCTION NEVUS. This form of pigmented nevus, well described by Ebert, by Traub and Keil and by Allen and Spitz, is characterized by the active formation of nevus cells in the lower epidermis—i.e., at the epidermal-dermal junction. There are two types of junction nevi between which, however, there are transitions. In one type, the newly formed nevus cells are present largely as well-circumscribed

nevus cell nests within the lower epidermis, while, in the other type, the nevus cells are scattered diffusely through the lower epidermis. This latter type of junction nevus has been called premalignant junction nevus by Allen and Spitz.

In junction nevi with well-circumscribed nevus cell nests in the lower epidermis, the residual epidermis appears essentially normal

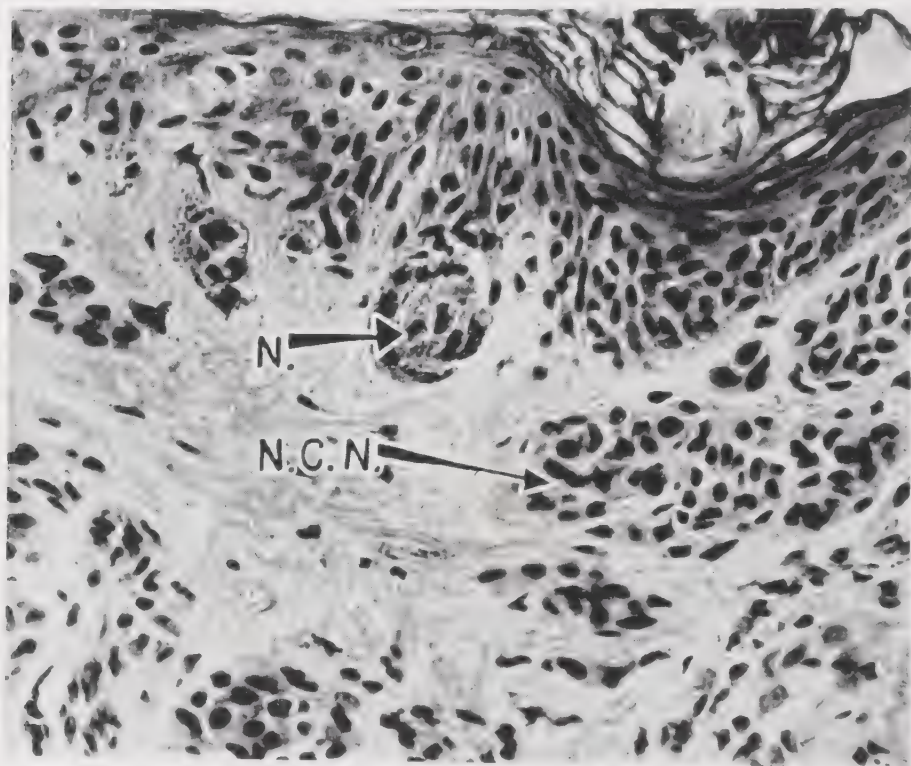


FIG. 247. Nevus pigmentosus, compound type. In the basal layer, one sees clear cells (melanocytes) lying singly and in nests. Those lying in nests have already the appearance of nevus cells. One nest (N.) is in the stage of "dropping off." In addition, typical nevus cell nests (N.C.N.) lie free in the dermis. Considerable amounts of melanin are present in the clear cells and in some of the nevus-cell nests. ($\times 200$)

(Fig. 244). Frequently, there are nests which lie beneath the epidermis but still are in contact with it and thus are in the stage of "dropping off." Occasionally, in other parts of the same nevus, one observes nevus cell nests located free in the dermis, representing a development into a compound nevus. The nevus cells contain varying amounts of melanin. Melanophores may be present in the dermis, but no inflammatory infiltrate is present. The nevus cells comprising the intra-epidermal nests have a regular, cuboidal appearance. In rare instances, however, they are spindle-shaped and endowed with stroma, so that they resemble schwannian cells and the cell nests

suggest Meissner tactile bodies (Fig. 245). Although all junction nevi have a certain potentiality to become malignant, because they are active nevi, the danger of malignant degeneration is slight in this type of junction nevus with its regularly formed nests of nevus cells.

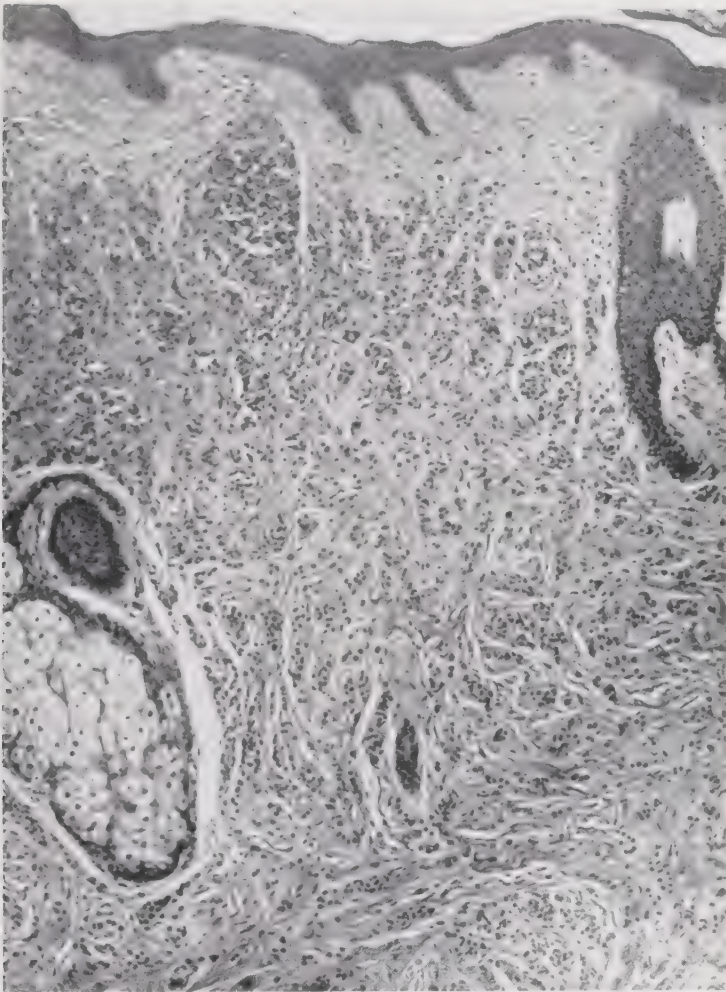


FIG. 248. Nevus pigmentosus, intradermal type. In the upper dermis, the nevus cells lie in nests and cords. In the lower dermis, the nevus cells are arranged more loosely and embedded in fibrous tissue. ($\times 100$)

In the second type of junction nevus, the premalignant junction nevus of Allen and Spitz, in which the nevus cells lie diffusely scattered in the lower epidermis, the lower epidermis appears disorganized by the presence of numerous vacuolated nevus cells with irregularly shaped nuclei (Fig. 246). The nevus cells usually contain a considerable amount of melanin. The border between the epidermis and the dermis is somewhat irregular, but no actual invasion of

nevus cells in the dermis is present. The upper dermis contains numerous melanophores and, in many instances, also a bandlike inflammatory infiltrate. This type of junction nevus is often difficult to differentiate from an early malignant melanoma (see page 459) and it is possible that it actually represents the earliest phase of a malignant melanoma. In any event, it possesses a definite potentiality to progress into a malignant melanoma.

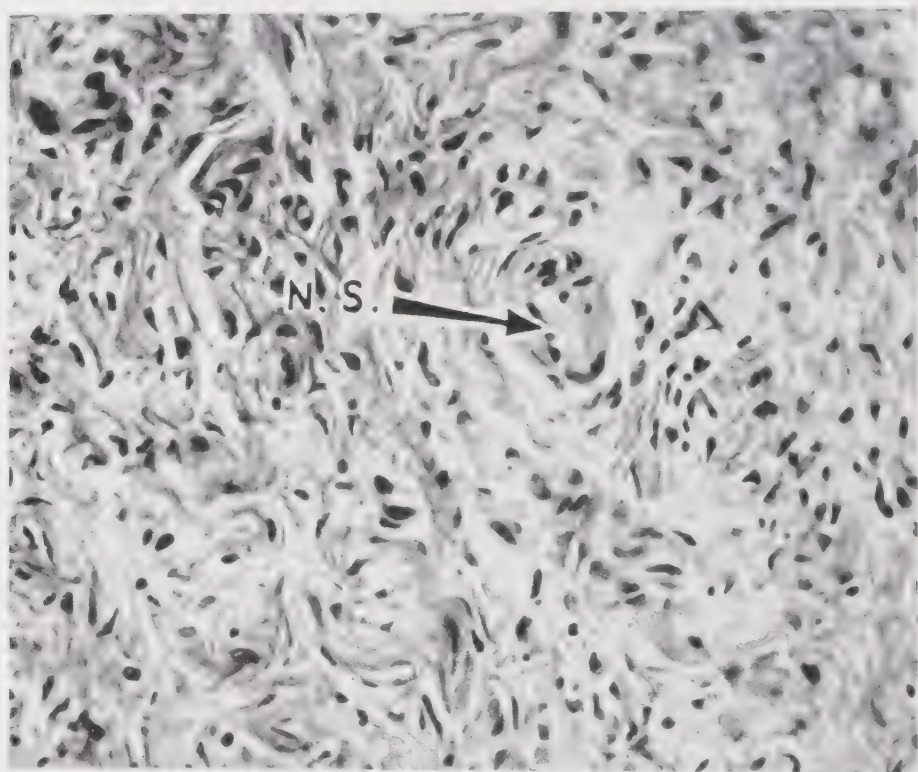


FIG. 249. Nevus pigmentosus, intradermal type. The lower dermis is shown. The nevus cells are largely spindle-shaped. They are embedded in fibrous tissue which has the same loose, wavy, pale appearance as in neurofibroma. In the center, one sees a neuroid structure (N.S.) resembling a Meissner tactile body. ($\times 200$)

COMPOUND NEVUS. In a compound nevus, one observes features of both junction nevus and intradermal nevus. Nevus cell nests are seen within the epidermis, dropping off from the epidermis, as well as in the dermis free from contact with the epidermis (Fig. 247).

INTRADERMAL NEVUS. Intradermal nevi show, in the upper dermis, nests and cords of nevus cells surrounded by bundles of collagen (Fig. 248). In some instances, the nevus cells lie in dense masses. Not infrequently, one encounters multinucleated nevus cells showing either clumping or rosette-like arrangement of small, darkly staining nuclei. These giant cells occur only in well-matured nevi and, there-

fore, can be taken as evidence of the benign nature of the nevus in which they occur. They should not be confused with the giant cells occurring in so-called juvenile melanoma and, occasionally, in malignant melanoma (see page 462). The nevus cells in the upper portion of the dermis frequently, though not always, contain melanin. In the presence of much melanin, melanophores are often present.

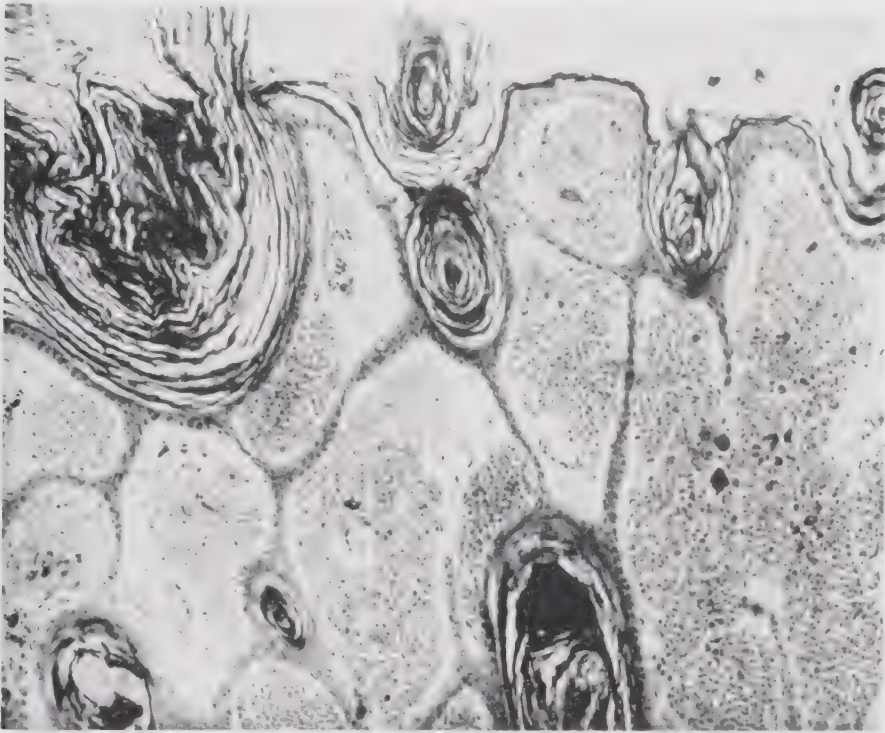


FIG. 250. Verrucous nevus pigmentosus. There is lacelike downward growth of the epidermis around nests of nevus cells. There are numerous multinucleated nevus cells. (This is not a sign of malignancy.) ($\times 100$)

No inflammatory reaction is present except in the case of mechanical irritation or of secondary infection. In that case, the inflammatory infiltrate, however, is focal rather than bandlike or diffuse as it is in malignant melanoma.

In the lower dermis, the nevus cells lie farther apart, tend to be spindle-shaped and are embedded in fibrous tissue. The fibrous tissue may have the same loose, wavy, pale appearance as in neurofibroma (Cohen). Within this fibrous tissue, the nevus cells may be arranged in narrow columns so that they suggest neural sheaths ("neuroid tubes" of Masson). In other areas, the fibrous tissue may be in concentric arrangement ("lames foliacées" of Masson) resulting in structures resembling Meissner tactile bodies (Fig. 249). Montgomery and

Kernohan found such structures in 11 per cent of their material of pigmented nevi. With special nerve stains such as the Bodian stain, one frequently can see nerve fibers in the fibrous tissue. They may occasionally be seen in close relation to the *lamelles foliacées*.

An occasional intradermal nevus is devoid of nevus cell nests in the upper dermis and shows only spindle-shaped nevus cells embedded in abundant fibrous tissue. Differentiation from a neurofibroma may then be difficult on a histologic basis (Cohen; Becker). Such nevi are referred to as neural nevi.

The epidermis over intradermal nevi may be normal, but often is flattened because of pressure from below. In some nevi, the epidermis shows hyperkeratosis, papillomatosis and lacelike downward growth (*verruccous nevus pigmentosus*) (Fig. 250). In others, large hair follicles are present (*nevus pigmentosus et pilosus*).

MALIGNANT MELANOMA

Malignant melanoma may arise as such or may develop from a pigmented nevus. If a malignant melanoma arises from a pigmented nevus, such nevus is almost invariably of the junction type. Clinical evidence that a malignant change is occurring in a pigmented nevus is presented by an increase in the size of the lesion, an increase in the depth of pigmentation and, not infrequently, the development of an inflammatory border with or without "spilling of pigment" from the lesion into the surrounding skin.

Early malignant melanoma is characterized by a gradually enlarging, deeply pigmented nodule, usually surrounded by erythema. Later, the lesion becomes fungating and satellite lesions may appear. Ulceration is a late symptom. In occasional instances, hyperpigmentation is slight or absent.

Metastasis takes place at first through the lymphatics, resulting in involvement of the regional lymph nodes. Blood spread is a late event and may be absent until nearly the end. When it occurs, metastases are usually widespread. The liver, the lungs, the brain and the skin are the most common sites of hematogenous metastases.

Malignant melanoma is rare before puberty and when it occurs it is usually clinically benign. For instance, in a series of 13 histologically malignant melanomas in children, published by Spitz, only one death occurred.

Histopathology. The malignant changes invariably begin at the dermal-epidermal junction, irrespective of whether a malignant melanoma starts as such or develops from a pigmented nevus (Miescher). For this reason, pigmented nevi with considerable junction activity, like the junction nevus, predispose to the development of malignant

melanomas, whereas intradermal nevi, which show little or no junction activity, give rise to a malignant melanoma very rarely. Especially the so-called premalignant junction nevus which is characterized by a diffuse arrangement of the nevus cells in the lower epidermis without tendency to nesting and by an inflammatory infiltrate in the upper dermis has a definite tendency to become malignant.

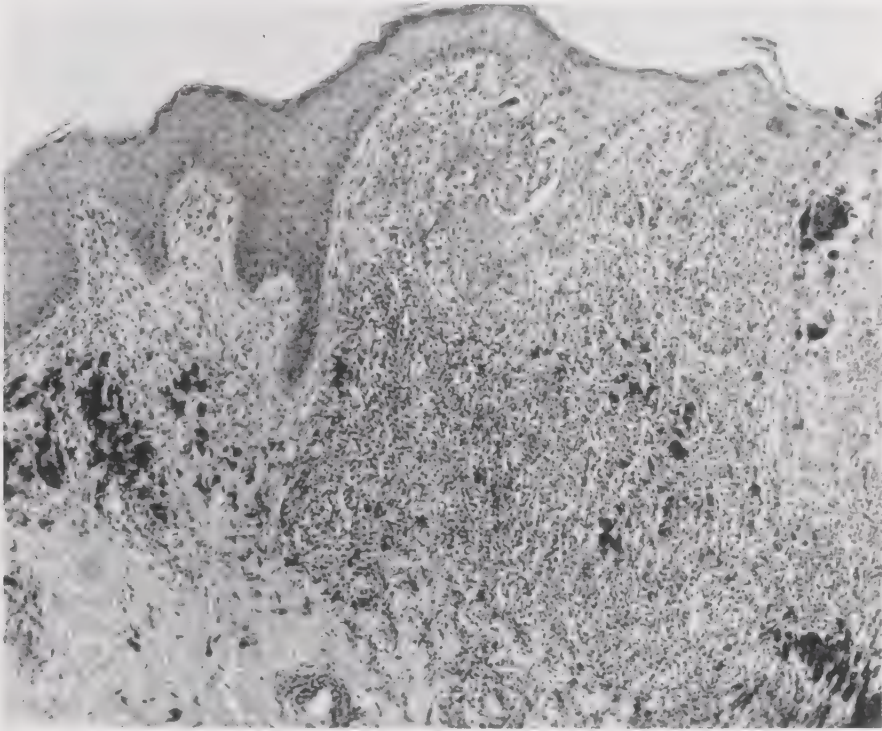


FIG. 251. Margin of an early malignant melanoma. On the left, the epidermis is normal. In the center, because of the presence of many atypical nevus cells, the epidermis appears disintegrated. On the right, one sees beginning invasion of the dermis by atypical nevus cells. The upper dermis shows a dense, bandlike inflammatory infiltrate intermingled with numerous melanophores. This infiltrate extends on the left, beyond the margin of the tumor under the normal epidermis. ($\times 100$)

In an early malignant melanoma, and at the advancing border of older lesions, one may find considerable changes within the epidermis but only slight invasion of the dermis by tumor cells. The lower epidermis, because of the presence of numerous atypical nevus cells, appears vacuolated, torn apart and even disintegrated (Fig. 251). This type of early malignant melanoma greatly resembles the premalignant type of junction nevus and differs from it only by the greater atypicality of the cells and the beginning invasion into the dermis (see also "Differential Diagnosis"). As in the premalignant

type of junction nevus, one finds in the upper dermis, close to the epidermis, a dense, bandlike inflammatory infiltrate intermingled with many melanophores. This inflammatory infiltrate often extends for a distance away from the malignant melanoma under the normal

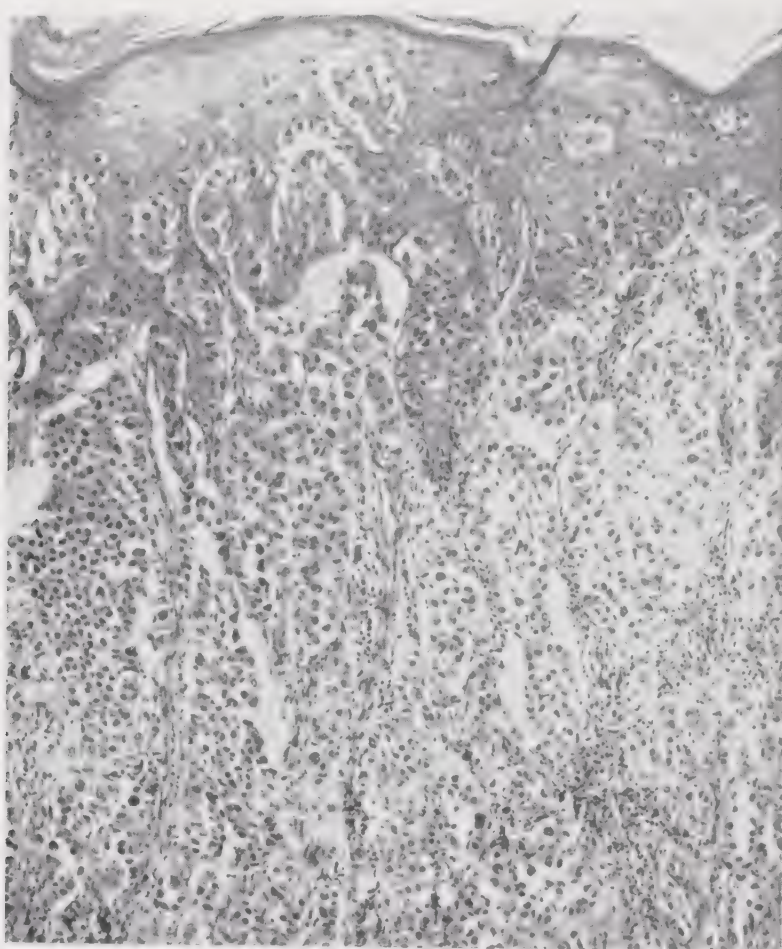


FIG. 252. Malignant melanoma. Low magnification. There is considerable junction activity. One finds not only dropping off of nevus cells and nevus cell nests downward into the dermis, but also migration upward into the stratum malpighii. The tumor cells are largely of the cuboidal type and lie in alveolar formations. ($\times 100$)

epidermis (Fig. 251). It is of interest that, once deep invasion of the dermis by the malignant melanoma cells has taken place, the inflammatory infiltrate tends to lessen; and in well-progressed malignant melanoma it is apt to be entirely absent, except at the margins if there is extension of the tumor.

In an advanced malignant melanoma, there is also considerable irregular junction activity (Fig. 252). The epidermis contains large,

irregularly shaped, often deeply pigmented nests of atypical nevus cells which may show mitotic figures (Fig. 253). The upper epidermis may be invaded and become so permeated with tumor cells that it

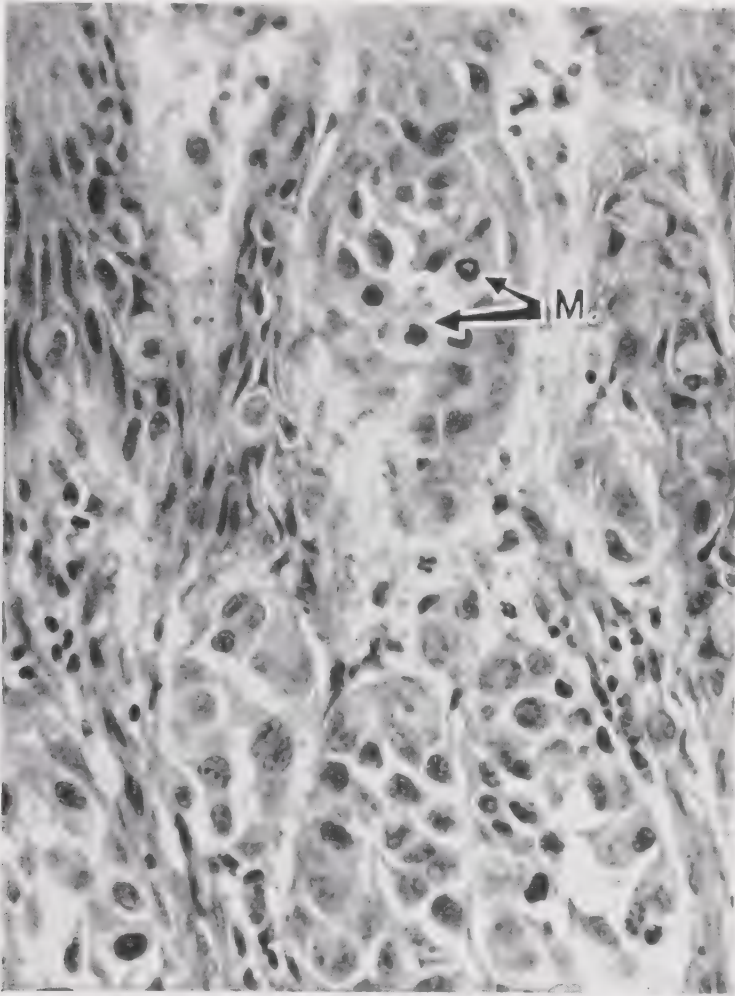


FIG. 253. **Malignant melanoma.** High magnification of Figure 252. The field shows the epidermal-dermal junction. The majority of tumor cells are cuboidal, but some are fusiform. There are several mitotic figures in the tumor cells (M.). ($\times 400$)

disintegrates and ulceration results (Fig. 254). In addition, there is deep penetration of the dermis by atypical nevus cells. Simultaneously with the downward penetration of the nevus cells, the epidermis may show considerable irregular downward proliferation of the rete ridges. The rete ridges may appear as if drawn down by the downward migration of the tumor cells.

The size and the shape of the tumor cells in the dermis show great

variation. Nevertheless, two types of cells can be recognized clearly, a cuboidal and a fusiform type. Although most tumors show both cell types, almost invariably one type greatly predominates. Predominance of cuboidal cells is much more common than predominance of fusiform cells. The cuboidal cells tend to lie in alveolar formations (Figs. 252 and 253). The fusiform cells tend to lie in irregular branching strands (Fig. 255). Tumors in which fusiform cells predominate

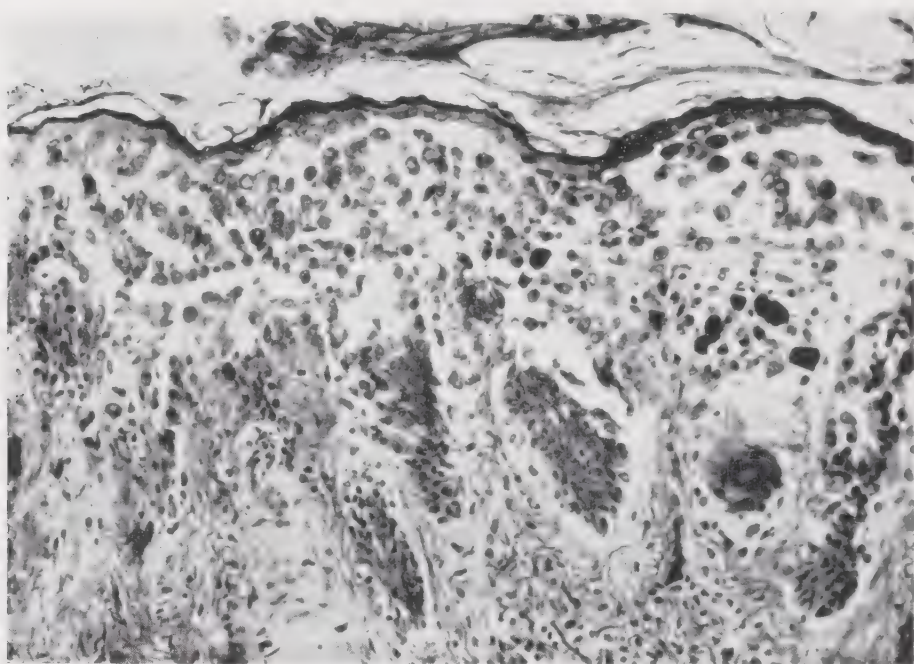


FIG. 254. Malignant melanoma. The epidermis has disintegrated due to permeation with tumor cells. ($\times 200$)

resemble fibrosarcoma but differ from it by the presence of junction activity. Mitotic figures are usually present in malignant melanoma, but often only in small numbers. They should be searched for, because their presence is of great value as evidence that the tumor is malignant, inasmuch as in pigmented nevi mitotic figures are very rare or absent (Miescher). Bizarre multinucleated giant cells occur occasionally.

The amount of melanin varies considerably in malignant melanomas. In some tumors, considerable amounts of melanin are present in both tumor cells and melanophores. In others, particularly in rapidly growing tumors, there may be no evidence of melanin in hematoxylin-eosin stains. Such tumors have been referred to as amelanotic malignant melanoma. However, staining of sections with silver will reveal in most instances a few cells containing melanin. Irrespective of the amount of melanin present, the dopa reaction

in malignant melanoma usually is strongly positive in the cells near the dermo-epidermal junction. The tumor cells deep in the dermis, however, react weakly or not at all (Miescher).

In children, malignant melanoma is uncommon and even lesions which histologically have the appearance of malignant melanoma

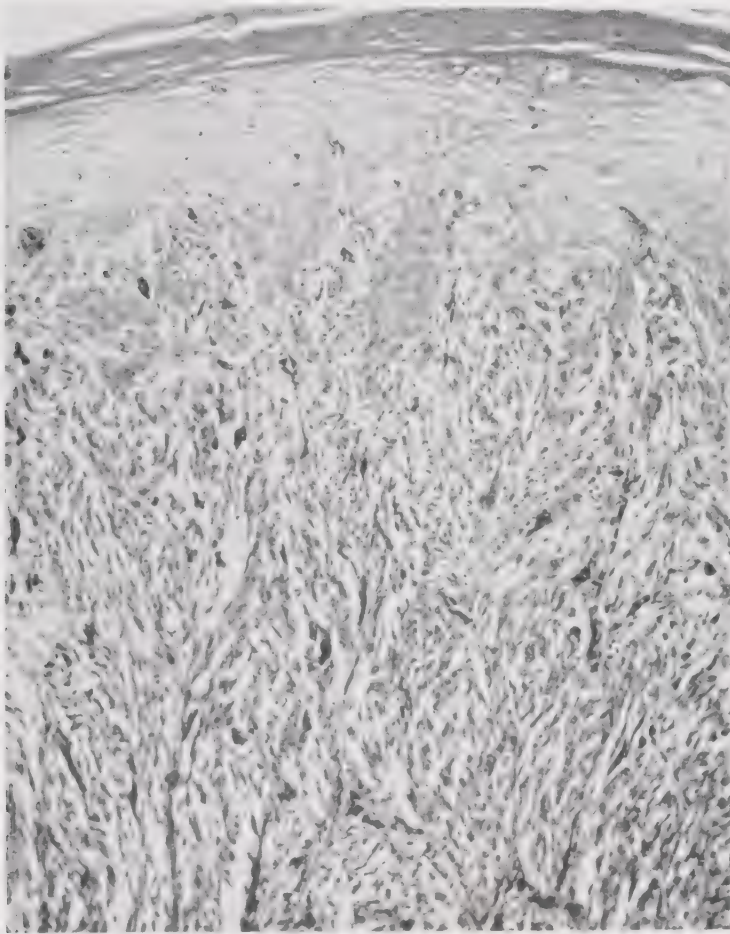


FIG. 255. Malignant melanoma. The tumor cells are fusiform and lie in irregular strands. The tumor thus resembles a fibrosarcoma, but differs from it by the presence of junction activity and of considerable amounts of melanin, which are located in tumor cells as well as in melanophores. ($\times 100$)

cause metastases only in the rarest instances. These malignant melanomas, generally referred to as juvenile melanomas, differ in their histologic aspects from malignant melanoma of adults in one point: In about one half of the cases of juvenile melanoma peculiar tumor giant cells are present such as do not occur in adult malignant melanoma (Spitz; Haber). These giant cells have a round, oval or stellate

shape and an acidophilic cytoplasm with one or more large, vacuolated, irregularly outlined nuclei. They differ from the giant cells of intradermal nevi, which have small, deeply basophilic nuclei, and from those found occasionally in malignant melanoma, which are larger and more bizarre.

The histologic appearance of metastatic lesions of the skin differs from that of primary lesions by the absence of junction activity. Metastatic lesions never show any inflammatory infiltrate (Dixon).

Differential Diagnosis. Differentiation of early malignant melanoma from junction nevus may cause considerable difficulties. That is easily explainable: a junction nevus may develop into a malignant melanoma. If this development proceeds slowly, as it often does, tumors in an intermediate stage of development result. The type of junction nevus most likely to undergo malignant degeneration is the one with diffusely scattered nevus cells in the lower epidermis, the so-called premalignant junction nevus (page 455, Fig. 246). This type of junction nevus, like early malignant melanoma, has numerous vacuolated nevus cells with atypical nuclei in the lower epidermis which thus appears disorganized. It may show, in addition, a bandlike inflammatory infiltrate in the upper dermis. It differs from malignant melanoma by the absence of invasion of the nevus cells into the dermis and by the absence of mitotic figures. However, these are not absolutely reliable criteria, and in some instances a decision as to whether malignancy exists already is impossible. There are some authors, like Miescher, who are inclined to regard as malignant any junction nevus showing a bandlike inflammatory infiltrate. According to Miescher, this is evidence that aggressive invasion is being fought off. It matters little, however, whether such junction nevi are called "pre-malignant" or "early malignant"; it is important that they require wide excision.

A highly malignant amelanotic melanoma may be difficult to differentiate from a highly malignant fibrosarcoma or a Grade IV spindle-cell squamous-cell carcinoma. For their differentiation, see under "Fibrosarcoma," page 410.

LENTIGO

Lentigo is a smooth, not infiltrated, dark-brown mark usually measuring only a few millimeters in diameter. A juvenile and a senile type occur. Juvenile lentigines begin to appear in childhood and occur on all parts of the body. Senile lentigines ("liver spots") occur in old age on the dorsa of the hands, on the forearms and on the face. Both types are benign. Clinical differentiation from junction nevus may be impossible.

Histopathology. The histologic findings are the same in juvenile and senile lentigo. The rete ridges appear elongated and club-shaped (Fig. 256). Eccentric thumb-like buds may project from them (Zeisler and Becker; Cawley and Curtis). The basal layer of the projecting rete ridges shows considerable hyperpigmentation and a great increase in the number of clear cells. No junction activity, i.e., "dropping-off" of clear cells, is observed. The upper dermis often contains melano-

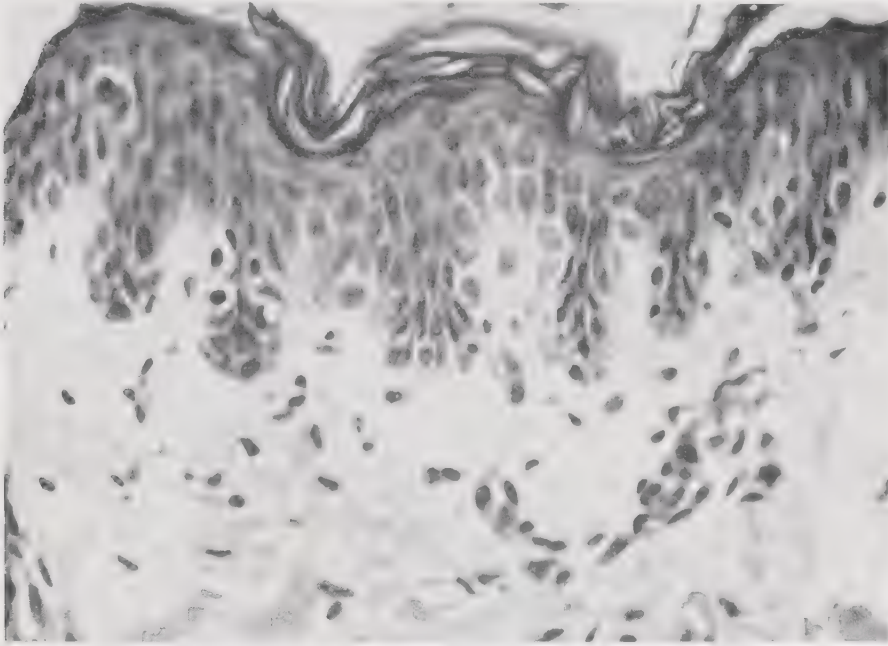


FIG. 256. **Lentigo.** The rete ridges are elongated. Numerous clear cells (melanocytes) are present in the basal layer. ($\times 200$)

phores and, sometimes, a mild perivascular lymphocytic infiltrate. In the case of senile lentigo, the upper dermis also shows basophilic degeneration of the collagen.

Whether or not lentigo can progress, by the onset of dropping-off activity, into a junction nevus is not yet fully decided; but this appears likely since junction nevi not infrequently show, at their periphery, the histologic picture of lentigo.

Differential Diagnosis. Lentigo must be differentiated from ephelis (freckle). Ephelides show hyperpigmentation of the basal layer but no elongation of the rete ridges.

MONGOLIAN SPOT

The typical Mongolian spot occurs as a bluish gray discoloration in the lumbosacral region. It is found with great regularity in mem-

bers of the Mongolian race but occurs occasionally also in other races. It is present at birth and gradually fades.

Occasionally, Mongolian spots occur outside the usual location as aberrant Mongolian spots (Cole, Hubler and Lund). They may even be multiple (Carleton and Biggs) or appear during adult life and gradually increase in size (Pariser and Beerman).

Histopathology. The dermis shows, especially in its midportion, fusiform and stellate cells filled with brown pigment granules. These cells lie widely scattered as well as in small groups. They give a positive dopa reaction (see page 12), indicating that they are melanocytes (Cole, Hubler and Lund).

Formerly, the cells composing the Mongolian spot were regarded as mesodermal melanocytes, as opposed to the epidermal melanocytes forming pigmented nevi. However, the theory of the neural origin of melanocytes has done away with this artificial division into epidermal and mesodermal melanocytes. The cells of the Mongolian spot (as well as those of the blue nevus—see below) are now regarded as melanocytes which in their embryonal migration from the neural crest to the epidermis failed to reach the epidermis but became arrested in the dermis (Montgomery).

BLUE NEVUS

The blue nevus is a sharply circumscribed, round or oval, soft nodule of slate-blue or bluish black color which measures, as a rule, only a few millimeters in diameter. There usually is only one lesion, although multiple blue nevi do occur. In rare instances, large, infiltrated plaques have been encountered (Upshaw, Ghormley and Montgomery). Malignant degeneration of blue nevi is very rare, but it does occur (Montgomery and Kahler; Allen and Spitz). Metastases may develop and cause death.

Histopathology. The cells composing blue nevi are of the same type as those composing the Mongolian spot. They are dopa-positive melanocytes which became arrested in the dermis during their embryonal migration from the neural crest to the epidermis (Montgomery). The number of these cells is, however, much greater in blue nevi than in the Mongolian spot.

In the blue nevus, greatly elongated melanocytes lie grouped in irregular masses and bundles in the middle and the lower thirds of the dermis (Fig. 257). Occasionally, these cell masses extend into the subcutaneous layer or close to the epidermis. The epidermis, however, is normal. The melanocytes are spindle-shaped and have long, bipolar, occasionally branching processes (see Plate I). They lie predominantly with their long axis parallel to the epidermis. Most of

them are filled with numerous fine granules of melanin, often so completely that their nucleus cannot be visualized. In addition, melanophores (chromatophores) frequently occur within and beside the masses of melanocytes. The melanophores differ from the melanocytes by being shorter and thicker and by containing coarser granules (Fig. 258). In addition, the melanocytes are dopa-positive while the melanophores are dopa-negative.

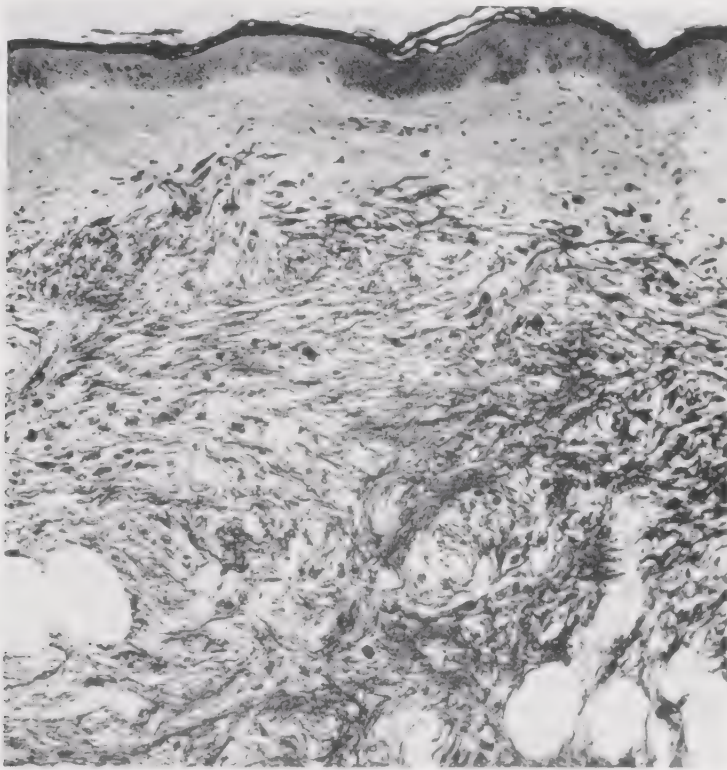


FIG. 257. **Blue nevus.** Low magnification. Numerous spindle-shaped melanocytes, filled with melanin, lie grouped in irregular bundles in the middle and the lower thirds of the dermis and in the subcutaneous fat. ($\times 50$)

Blue nevi may undergo fibrosis. In that case, thick bundles of collagen separate the melanocytes. In occasional instances, the presence of a pigmented nevus and of a blue nevus in the same lesion has been reported (Montgomery and Kahler).

The blue color which the blue nevus presents clinically results from the deep location of the pigment beneath an opaque medium represented by the normal epidermis and the upper dermis.

In addition to the standard features of malignant alteration (such as pleomorphism, mitotic figures and large, irregularly hyperchromatic nuclei), blue nevi in which malignant degeneration has oc-

curred show areas of necrosis as a diagnostically important feature (Allen). The malignant cells may appear swollen and vacuolated and may lose their spindled character so that recognition of the lesion as

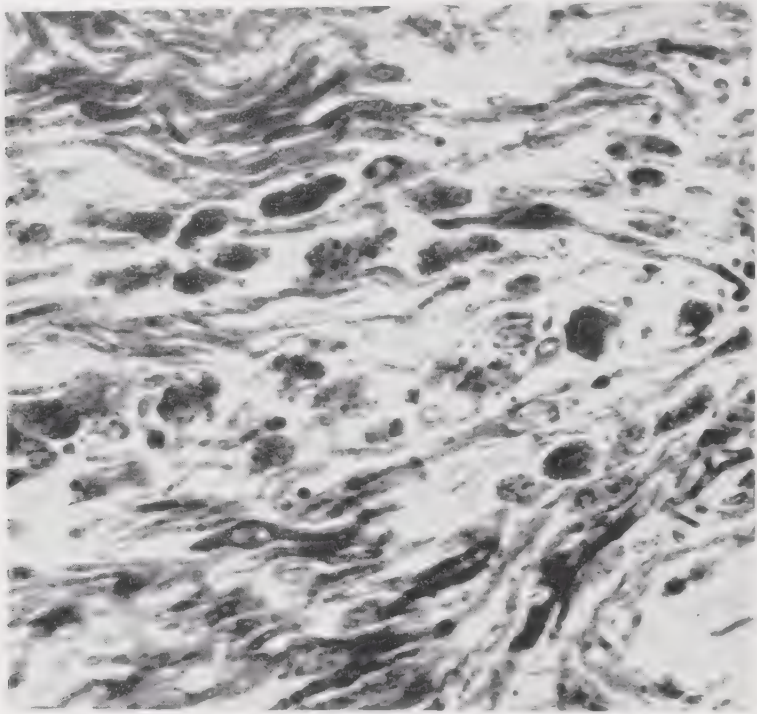


FIG. 258. **Blue nevus.** High magnification of Figure 257. There are numerous spindle-shaped melanocytes filled with fine melanin granules. In addition, melanophores filled with large, irregularly shaped melanin granules are present in the middle third of the field shown. ($\times 400$)

a malignant blue nevus must be based on the presence of residual portions of the original, benign blue nevus.

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21

Lymphoma and Myelosis

Lymphoma designates a group of malignant tumors arising, usually in multiple foci, from the lymphoid-reticular system. Myelosis is a designation for malignant tumors arising, invariably in multiple foci, from the myeloid system.

LYMPHOMA

Lymphomas are composed primarily of immature and mature cells of the lymphoid-reticular system. The mother cell of the lymphoid-reticular system is the lymphoid-reticular stem cell. This cell may differentiate into a lymphoid cell (lymphoblast to lymphocyte) or into a reticular cell (reticulum cell to histiocyte to fibroblast) (see Chart 2, page 33). The type of lymphoma which results in a given case depends on the degree of immaturity of the cells and on the direction of their differentiation.

The lymphomas may start as a solitary lesion and may remain as such for a long period of time. As a rule, however, the lesions are multiple from the beginning. The multiplicity of the lesions is due to the systemic nature of the disease and usually not to metastasis. Occasionally, however, dissemination by metastasis occurs in addition.

Leukemia is frequent with some types, rare with other types of lymphoma. Leukemia is merely the result of a release of immature tumor cells into the blood stream and does not represent a separate form of disease. Invariably, one finds in patients with leukemia involvement of the bone marrow. However, marrow involvement may occasionally be found in patients with normal blood pictures (Gall and Mallory).

Just as leukemia is a part of the disease which may be present or absent, so involvement of the skin is a variable manifestation of lymphoma, found more frequently in some forms of lymphoma than in others, but a possible occurrence in all. In a review of 618 cases of lymphoma, Gall and Mallory found leukemic blood changes in 17 per cent of the cases and cutaneous lesions in 20 per cent.

The lymphomas may be divided on a histologic basis into two main groups, the monomorphous and the polymorphous group. In the

former, the tumors are composed entirely of lymphoid-reticular cells, while, in the latter group, the tumors show an admixture of inflammatory cells. The following classification, which is based on that by Gall and Mallory, is suggested:

Monomorphous group:

1. Stem-cell lymphoma.
2. Reticulum-cell lymphoma.
3. Lymphoblastic lymphoma.
4. Lymphocytic lymphoma.
5. Follicular lymphoma (Brill-Symmers).

Polymorphous group:

6. Hodgkin's disease.
7. Mycosis fungoides.

It is impossible to assign every case of lymphoma to one of these seven types, because some tumors are in an intermediary stage of differentiation or show features of more than one type. Furthermore, different types of lymphoma may be encountered in different areas of the same patient and, not infrequently, as the disease progresses, the lesions may become less differentiated and require reassignment to another type (Keim; Gall and Mallory; Herbut, Miller and Erl).

The terms round-cell sarcoma, lymphosarcoma and reticulum-cell sarcoma formerly were and occasionally still are used as designation for single tumors of lymphoma. The use of the term sarcoma is misleading, however, because, even in the case of a single lesion, the potentially systemic nature of the disease may become apparent at any time. If new lesions arise, they usually do not represent metastases, as they would in a true sarcoma, but independent foci.

Clinical Appearance. The cutaneous manifestations of lymphoma can be divided into specific and nonspecific lesions. Nonspecific lesions, which when found in association with leukemia are often referred to as leukemids, may consist of macules, papules, purpuric lesions, vesicles, bullae, eczematous lesions and exfoliative dermatitis. Specific lesions may consist of plaques, nodules and tumors; in addition, however, any of the lesions mentioned as occurring as a non-specific reaction may show a specific lymphomatous infiltrate. This holds true especially of eczematous lesions and exfoliative dermatitis. Thus, it is impossible to predict always from the clinical appearance whether a lesion is nonspecific or specific.

Histopathology. Histologically, specific lesions of lymphoma of the skin show either large masses of lymphoma cells, patchy accumulations of lymphoma cells or an inflammatory infiltrate intermixed with lymphoma cells. The lymphoma cells vary with the type of lymphoma and may be immature lymphoid-reticular cells, such as

stem cells, reticulum cells and lymphoblasts, or mature lymphoid-reticular cells, such as histiocytes and lymphocytes. Usually, atypical cells and a varying number of mitotic figures are present. Nonspecific lesions consist of an inflammatory infiltrate without immature cells.

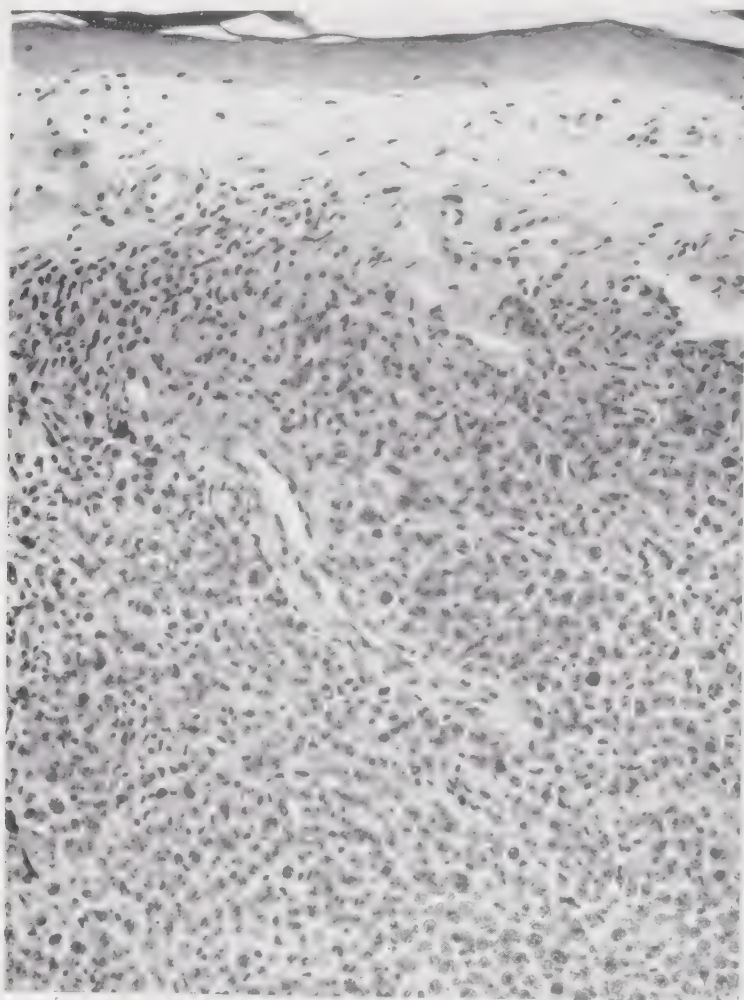


FIG. 259. Stem-cell lymphoma. Low magnification. A large mass of loosely packed tumor cells is present in the dermis. ($\times 100$)

It is probable that most if not all nonspecific lesions result from lymphoma cells (Gates). It may be assumed that the lymphoma cells either have been overwhelmed and removed by the inflammatory infiltrate which they themselves have provoked or do not differ sufficiently in their appearance from the inflammatory cells to be recognized as lymphoma cells.

Large masses of lymphoma cells in the dermis and the subcutaneous layer, which clinically appear as cutaneous tumors, may occur in all

forms of lymphoma. They occur most commonly in stem-cell lymphoma, reticulum-cell lymphoma, lymphoblastic lymphoma and in the tumor stages of Hodgkin's disease and mycosis fungoides. The tumor masses may be sharply demarcated, but usually there are small, outlying islands of tumor cells and, in addition, single rows of lym-

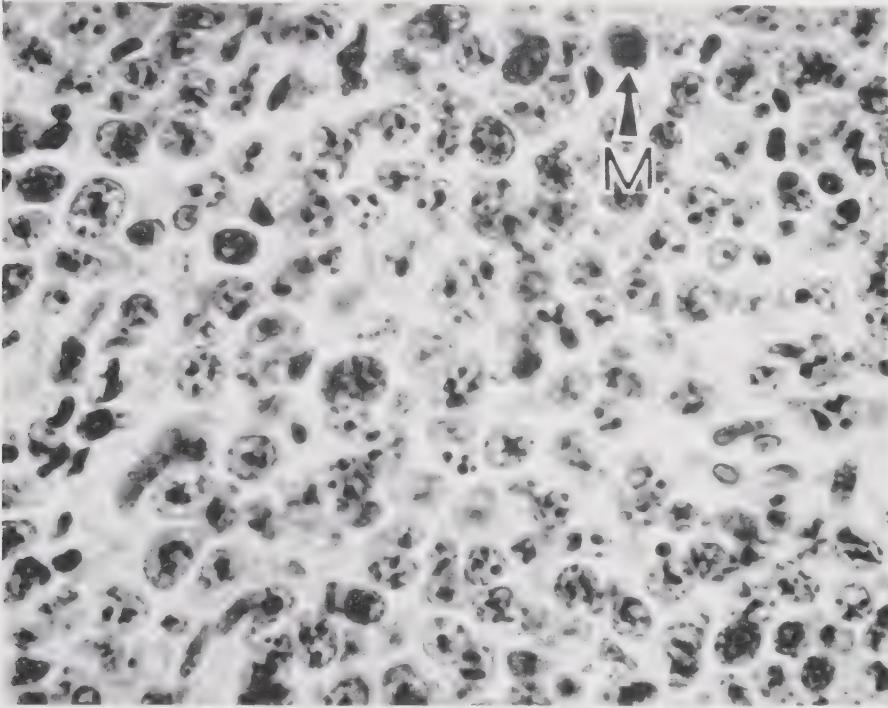


FIG. 260. Stem-cell lymphoma. High magnification of Figure 259. The tumor cells possess abundant, pale-staining cytoplasm and large, round nuclei. The nuclei contain delicate, dustlike chromatin and one or several prominent nucleoli. Mitotic figures are numerous. A large, atypical mitotic figure (M.) is present in the upper right corner. ($\times 400$)

phoma cells which extend from the main tumor mass into the spaces between collagen bundles, "like Indians in a file." (This phenomenon of single-row invasion also occurs in metastatic carcinoma of the skin, especially in cancer en cuirasse of the breast—see page 392.)

Patchy accumulations of lymphoma cells occur most commonly in lymphocytic lymphoma. The patches are distributed indiscriminately throughout the dermis and may occur even in the subcutaneous tissue. They usually show a blood vessel in their center around which the infiltrate lies as a thick sleeve.

An inflammatory infiltrate intermixed with tumor cells is the usual picture in Hodgkin's granuloma and in the erythematous and the

plaque stages of mycosis fungoides. This type of infiltrate, too, tends to have a patchy arrangement.

So-called nonspecific lesions, which show a nonspecific chronic inflammatory infiltrate, occur in the skin, particularly in early mycosis fungoides, in Hodgkin's disease and in lymphocytic lymphoma.

1. STEM-CELL LYMPHOMA

Stem-cell lymphoma produces, as a rule, tumorlike lesions. In about one third of the cases, it arises as a single lesion, either in the skin or elsewhere, and may remain localized for some time. Leukemia is very rare.

Histopathology. The lesions are composed of large masses of cells (Fig. 259). The vast majority of cells are stem cells, but most tumors show an admixture of reticulum cells. Stem cells are large in size and possess abundant, pale-staining cytoplasm. They may lie separate from one another, but frequently the cytoplasm of neighboring cells is fused. Their nuclei are large, from two to four times the size of a normal lymphocyte, round and filled with delicate, dustlike chromatin. They usually possess one but occasionally several large, deeply staining nucleoli (Fig. 260). Typical and atypical mitotic figures are numerous. Stem cells are too immature to form reticulum fibers (Gall and Mallory).

2. RETICULUM-CELL LYMPHOMA

Tumorlike lesions are the most common type. In about one third of the cases, reticulum-cell lymphoma, like stem-cell lymphoma, starts as a solitary lesion. Occasionally, the first lesion or group of lesions occurs in the skin (Director and Kern).

If leukemia develops in reticulum-cell lymphoma, it is of the monocytic variety, since the blood monocyte is derived from the reticular group of cells (Herbut and Miller). True monocytic leukemia is sometimes referred to as the Schilling type of monocytic leukemia, in contrast to the Naegeli type of monocytic leukemia in which monocyte-like cells arise from myeloblasts and which therefore is a form of myeloid leukemia (Montgomery and Watkins) (see page 495). In the presence of monocytic leukemia, the skin frequently shows purpuric, vesicular and papular lesions (Herbut and Miller). In addition, plaques and tumorlike lesions may be present (Wayson and Weidman). Exfoliative dermatitis may occur (Montgomery and Watkins). Swelling and ulceration of the gums are frequent.

Histopathology. In tumorlike lesions, large, compact masses of cells are present. The type cell is an immature reticular cell (reticulum cell). This cell is smaller than a stem cell but larger than a ma-

ture reticular cell (histiocyte). [The author prefers to call the immature reticular cell a reticulum cell, and the mature reticular cell a histiocyte. However, it should be kept in mind that many authors use the term reticulum cell also for the mature reticular cell (see page 35).] The reticulum cells in reticulum-cell lymphoma have an eosinophilic cytoplasm, the border of which tends to be irregular in

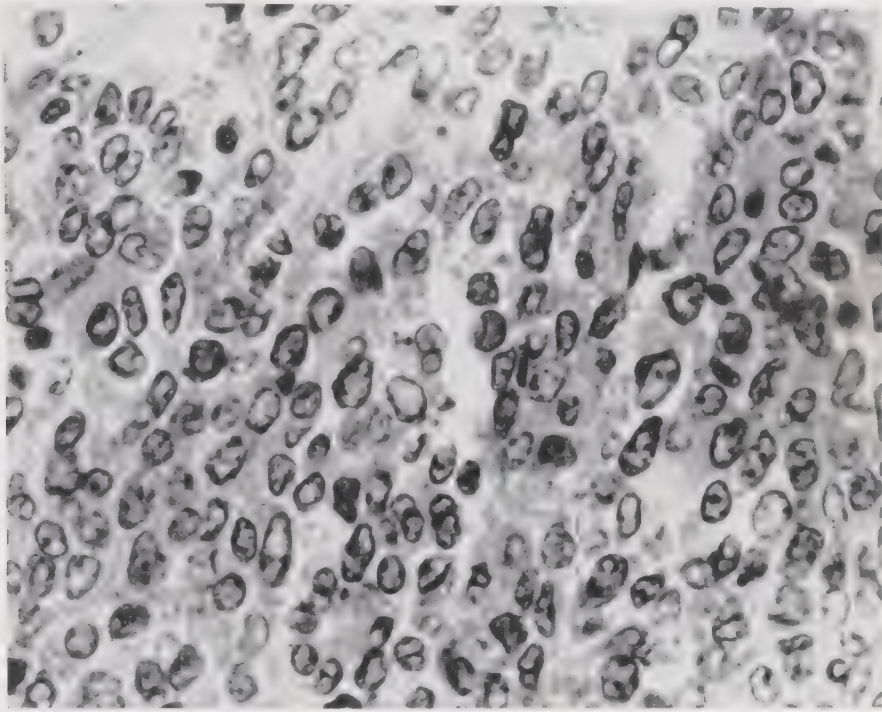


FIG. 261. Reticulum-cell lymphoma. The tumor cells possess abundant, pale-staining cytoplasm and variously shaped nuclei. Some are round, but most are oval or kidney-shaped. The nuclei are pale-staining and possess a distinct nuclear membrane. ($\times 400$)

outline, suggesting ameboid propensities. The nuclei differ in configuration; a few are round, more are oval and still others are kidney-shaped. They are pale-staining and appear vesicular because of the presence of a well-defined, strongly basophilic nuclear membrane (Fig. 261). They show a moderately heavy chromatin network; nucleoli are rarely evident. A moderate number of mitotic figures is present. The reticulum cells, being immature, form only a scanty reticulum network. In most tumors, a fair number of mature reticular cells (histiocytes) are present. Tumors containing many histiocytes may have a well-developed reticulum network. Lymphocytes are sometimes also found, presumably evidence of exudative reaction. (Wayson and Weidman; Gall and Mallory; Director and Kern.)

In small cutaneous lesions, as they occur particularly in association with monocytic leukemia, the infiltrate is less extensive and the cells are of smaller size. Nevertheless, the cells have the same appearance as in the large lesions having indented or kidney-shaped, pale nuclei with a distinct nuclear membrane (Hubler and Nether-

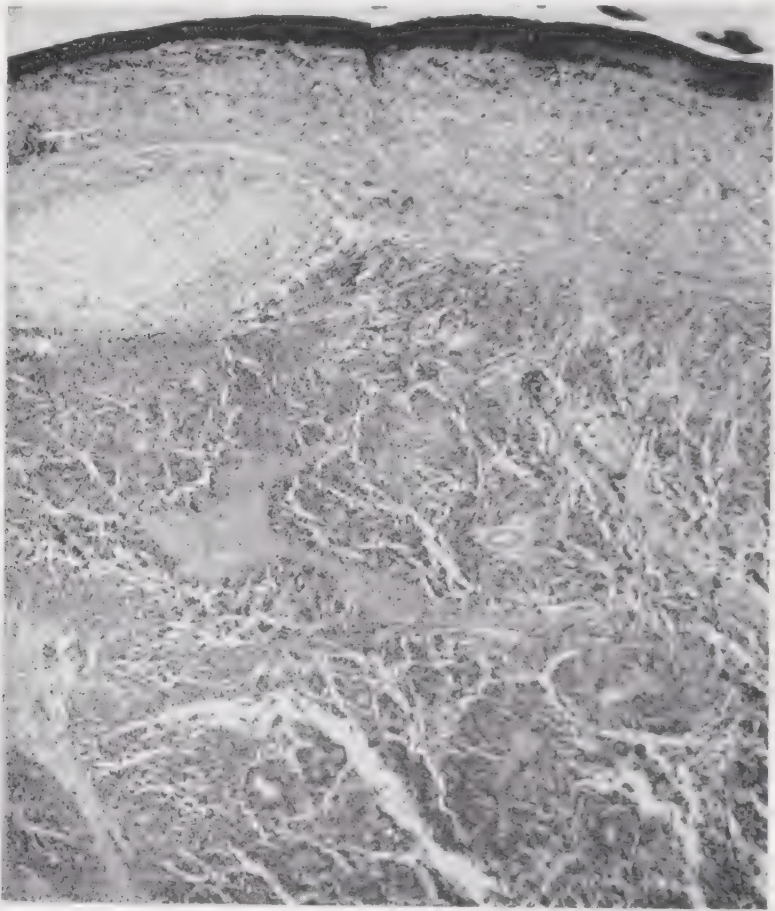


FIG. 262. Lymphoblastic lymphoma. Low magnification. Masses of densely packed tumor cells are present in the lower dermis. ($\times 50$)

ton). In the presence of monocytic leukemia, extravasation of erythrocytes is frequently found.

Differential Diagnosis. It is important not to confuse reticulum-cell lymphoma with reticulo-endotheliosis (histiocytosis) of the Letterer-Siwe and Hand-Schüller-Christian types (see page 262). Reticulum-cell lymphoma and reticulo-endotheliosis are occasionally so difficult to differentiate histologically that in the past they have been confused (Sweitzer, Winer and Cumming). Reticulo-endotheliosis, like reticulum-cell lymphoma, shows large, irregularly shaped reticular cells (histiocytes) but shows no atypical reticular cells, par-

ticularly no mitotic figures. The lesions contain, as a rule, eosinophils and one may find cholesterol deposits in the reticular cells.

3. LYMPHOBLASTIC LYMPHOMA

The cutaneous lesions consist predominantly of nodules, plaques and tumors. Purpura is not uncommon.

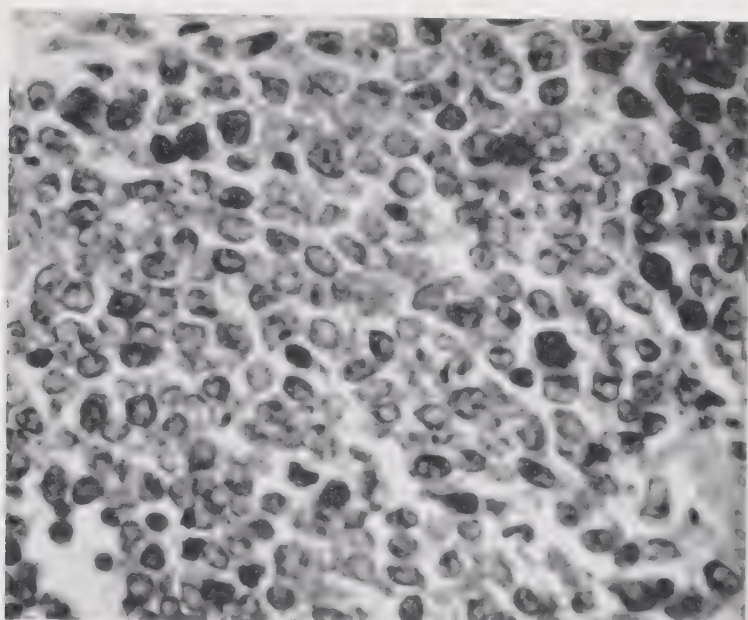


FIG. 263. Lymphoblastic lymphoma. High magnification of Figure 262. The cells have only little cytoplasm. The nuclei lie, therefore, more densely packed than in stem-cell lymphoma or reticulum-cell lymphoma. The nuclei contain evenly distributed particles of chromatin. They stain darker than the nuclei of reticulum cells but lighter than those of lymphocytes. A few lymphocytes are present. ($\times 400$)

Leukemia develops in a large percentage of cases—according to Gall and Mallory, in 40 per cent. The type is lymphatic leukemia.

Histopathology. The cutaneous lesions show usually large masses of tumor cells and occasionally a patchy infiltrate. Lymphoblasts predominate, but, in most lesions, stem cells and lymphocytes are present in moderate number. Lymphoblasts possess a narrow basophilic rim of cytoplasm and large, round or slightly indented nuclei. Because of the relatively small amount of cytoplasm, the nuclei lie close together, much closer than in stem-cell or reticulum-cell lymphoma (Fig. 262). The nuclei are larger than those of lymphocytes and more uniform in appearance than those of stem cells or reticulum cells. The chromatin in the nuclei of lymphoblasts is distributed rather evenly and much less clumped than in lymphocytes, giving the nuclei

a vesicular appearance (Fig. 263). Nucleoli are observed infrequently. Mitotic figures are usually numerous. A fine, evenly distributed reticulum framework is occasionally present (Gall and Mallory).

4. LYMPHOCYTIC LYMPHOMA

Cutaneous nodules, plaques and tumors occur. Exfoliative dermatitis is relatively common. In addition, nonspecific lesions, especially

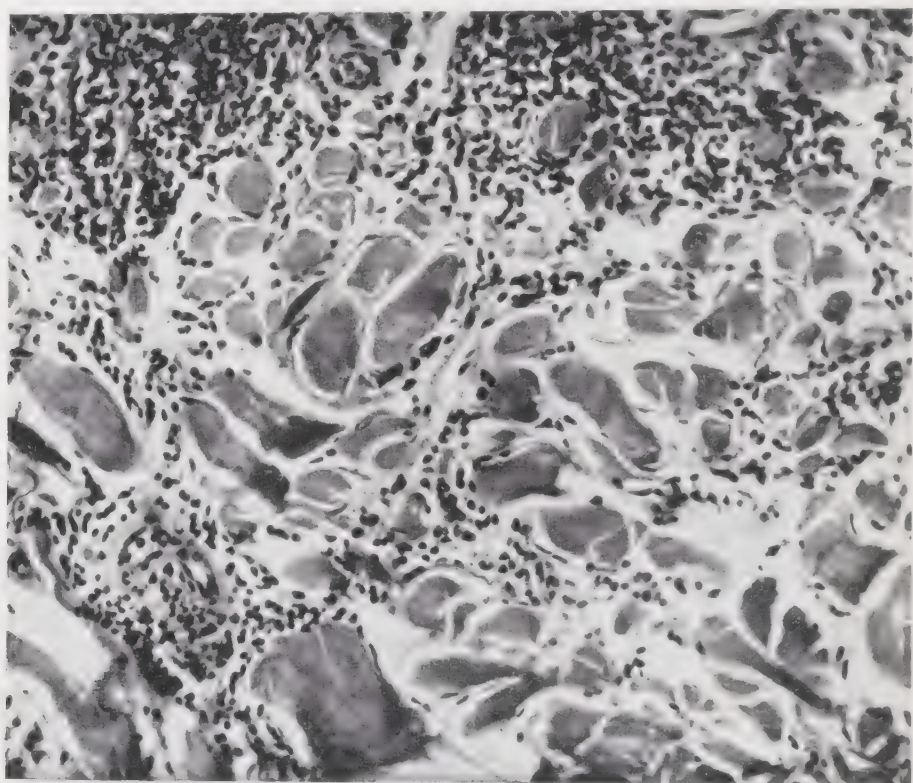


FIG. 264. Lymphocytic lymphoma. In the upper third of the photograph, one sees the periphery of a large mass of tumor cells. Rows of tumor cells extend from there between the collagen bundles. The cells are indistinguishable from normal lymphocytes. ($\times 200$)

papules and petechiae, may be observed. Of interest is the occasional occurrence of generalized herpes zoster in association with lymphocytic lymphoma (see page 491).

Lymphatic leukemia occurs in about half the cases of lymphocytic lymphoma (Gall and Mallory).

Histopathology. The specific cutaneous lesions may show either large masses of cells (Fig. 264), scattered patches of cells (Fig. 265) or, in the case of exfoliative dermatitis, a diffuse infiltrate in the upper dermis.

In lesions showing large masses or scattered patches of cells, the predominating cell is indistinguishable from a normal lymphocyte. Lymphoblasts may be present in small numbers. Mitotic figures are sparse. Thus, the infiltrate appears homogeneous. At the periphery of the large masses, one frequently sees rows of tumor cells extending between and even around intact collagen bundles in a similar way as it may be observed in scirrhous metastatic carcinoma.

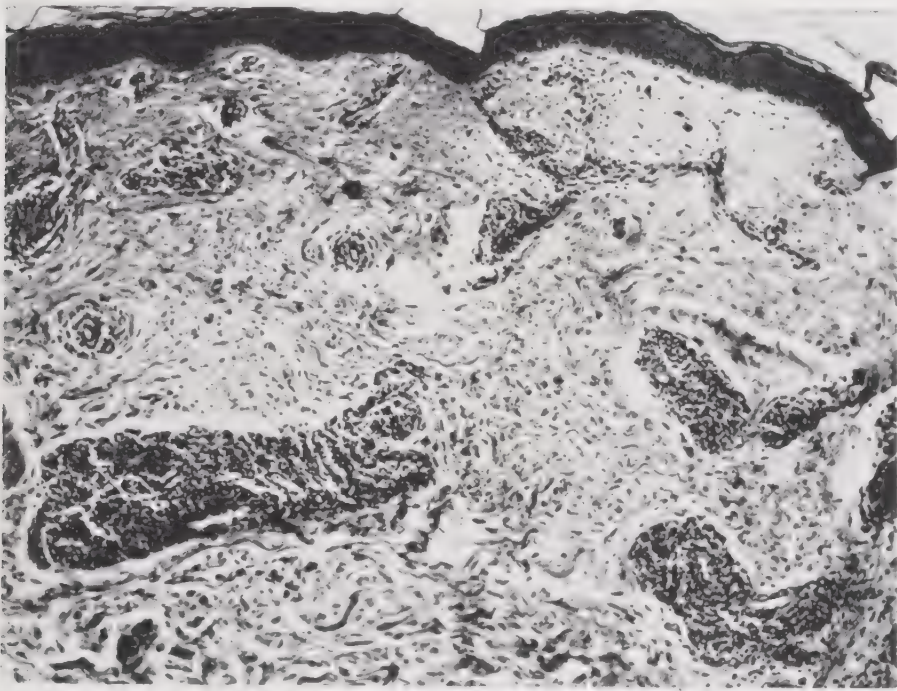


FIG. 265. Lymphocytic lymphoma. Sharply demarcated, large patches of lymphocytes are distributed through the dermis. Most patches show a blood vessel in their center. ($\times 100$)

If the infiltrate consists of scattered patches, some difficulty may arise in differentiating lymphocytic lymphoma from chronic discoid lupus erythematosus in which the infiltrate is also patchy. In lymphocytic lymphoma, however, the patches are distributed indiscriminately throughout the dermis, without predilection to the upper dermis and the vicinity of the cutaneous appendages. In addition, the patches are uniformly composed of lymphocytes without an admixture of plasma cells and histiocytes as in lupus erythematosus. Furthermore, the epidermal changes associated with lupus erythematosus are absent.

In instances of exfoliative dermatitis, one finds a diffuse infiltrate in the upper dermis. It is composed, in addition to lymphocytes, of

neutrophils, eosinophils and plasma cells, resulting in an inflammatory infiltrate of banal appearance. However, immature lymphocytes and mitotic figures here and there usually reveal the nature of the process. Sometimes one also finds in the lower cutis variously sized patches composed solely of lymphocytes, further facilitating the diagnosis (Keim).

5. FOLLICULAR LYMPHOMA (BRILL-SYMMERS)

Follicular lymphoma, also called Brill-Symmers disease, occurs predominantly in the lymph nodes, causing considerable enlargement of the affected lymph nodes. The skin is involved in only rare instances, showing discrete, firm, brownish to reddish nodules (Gall, Morrison and Scott).

Follicular lymphoma of the lymph nodes was described originally as a hyperplasia but is now generally regarded as lymphoma, because it may progress into other forms of lymphoma and is ultimately fatal.

Histopathology. The enlarged lymph nodes show replacement of the normal architecture by numerous round, follicle-like nodules of varying size. These follicles are composed of densely packed lymphoblasts and are surrounded by a thin rim of normal small lymphocytes. Mitotic figures are present within them in small number. Very frequently, the follicles are partially separated from the surrounding stroma by fissures. Although these fissures are an artefact caused by shrinkage of tissue during fixation, they are of considerable aid in the diagnosis of follicular lymphoma (Gall, Morrison and Scott).

The cutaneous lesions, in rare instances, show the same follicular pattern as the lymph nodes. Usually, however, the infiltrate has the appearance of either lymphocytic or lymphoblastic lymphoma.

Differential Diagnosis. Follicular lymphoma of the lymph nodes must be differentiated from reactive hyperplasia such as occurs in dermatopathic lymphadenitis (see page 75). It differs from the latter by the presence of mitotic figures, obliteration of the sinuses, absence of inflammatory cells and absence of phagocytosis.

Confusion of follicular lymphoma with dermatopathic lymphadenitis has caused several authors to describe erroneously the occurrence of generalized exfoliative dermatitis in Brill-Symmers disease (Combes and Bluefarb; Rost). These cases actually were instances of idiopathic generalized exfoliative dermatitis with secondary dermatopathic lymphadenitis.

For differentiation of follicular lymphoma from lymphocytoma cutis, see page 491.

6. HODGKIN'S DISEASE

In most instances, Hodgkin's disease affects primarily and predominantly the lymph nodes. In rare instances, the first lesions are noted in the skin (Reimann, Havens and Herbut).

Cutaneous lesions are observed quite frequently. Nonspecific lesions, however, are more common than specific lesions. Most commonly found are papular lesions, which are intensely pruritic. Other lesions are eczematous patches, generalized exfoliative dermatitis, nodules or tumors. The latter frequently undergo ulceration (Senear and Caro). Generalized herpes zoster occurs occasionally (see page 491).

Histopathology. In the specific lesions of Hodgkin's disease, two stages can be recognized, Hodgkin's granuloma and Hodgkin's sarcoma. Hodgkin's sarcoma may follow Hodgkin's granuloma, but the disease may show the morphology of Hodgkin's sarcoma at the onset (Jackson and Parker).

Hodgkin's granuloma is composed of a polymorphous infiltrate. The majority of the constituent cells are the usual components of a chronic inflammatory infiltrate, namely, eosinophils, neutrophils, lymphocytes, plasma cells, histiocytes and fibroblasts. In addition, tumor cells, namely, stem cells, immature and atypical reticulum cells and Sternberg-Reed giant cells are present. The Sternberg-Reed cells, which are pathognomonic of Hodgkin's disease, develop probably from stem cells. They occur as mononucleated and multinucleated cells. The mononucleated Sternberg-Reed giant cell possesses a very large, irregularly shaped nucleus. The multinucleated Sternberg-Reed giant cell has either a double nucleus ("mirror-image nucleus") or several nuclei of dissimilar size and shape clustered in the center of the cell. The nuclei of both mononucleated and multinucleated Sternberg-Reed cells contain a prominent nucleolus and heavy clumps of chromatin. Mitotic figures occur with moderate frequency in the stem cells, reticulum cells and Sternberg-Reed cells. Hodgkin's granuloma has a tendency to focal necrosis and in lesions showing this phenomenon phagocytes are quite numerous. Eosinophils are usually but not invariably present. In some cases, they constitute the predominant cell. Collagen production is the result of the natural evolution of maturing histiocytes into fibroblasts. Collagen production is scanty in the early phases and progresses steadily until broad fibrous septa separate the foci of cellularity into islands (Jackson and Parker).

Hodgkin's sarcoma differs from Hodgkin's granuloma by the preponderance of stem cells, reticulum cells and Sternberg-Reed cells

over all other elements comprising the tumor. Multinucleated cells and mitotic figures are numerous. Fibrosis is absent or minimal. Except for the presence of Sternberg-Reed cells, the histologic picture may greatly resemble that of stem-cell or reticulum-cell lymphoma (Gall and Mallory).



FIG. 266. Hodgkin's disease. Low magnification. There are two large masses of tumor cells. In addition, numerous small collections of tumor cells are present throughout the dermis. ($\times 50$)

The nodules and the tumors of the skin show large masses of cells in the dermis and not infrequently also in the subcutaneous fat (Fig. 266). The histologic picture is more apt to be that of Hodgkin's granuloma than that of Hodgkin's sarcoma and is rarely as typical as in the lymph nodes. The number of Sternberg-Reed cells, on the presence of which the diagnosis depends, is often small and fibrosis

is less pronounced. The presence of atypical reticulum cells with mitotic figures and of chronic inflammation may suggest mycosis fungoides. Even then, however, a thorough search of serial sections will usually show a few Sternberg-Reed giant cells (Fig. 267). It is important not to confuse clumped reticulum or endothelial cells with multinucleated Sternberg-Reed cells. Reticulum and endothelial

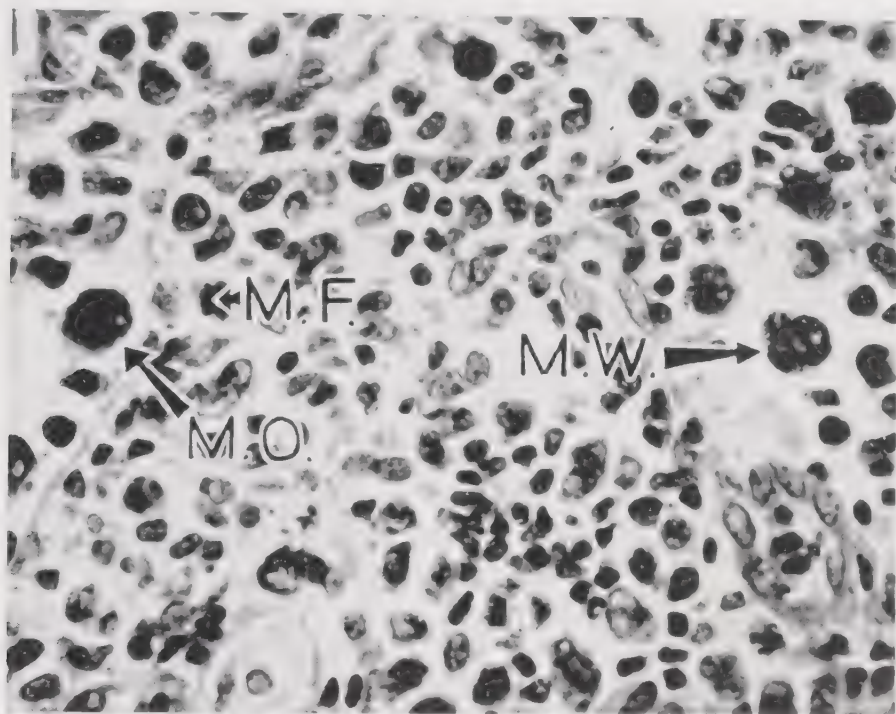


FIG. 267. Hodgkin's disease. High magnification of Figure 266. There is a dense, polymorphous infiltrate. It contains many atypical reticulum cells and several mitotic figures (M.F.). A mononucleated Sternberg-Reed giant cell (M.O.) is present on the left, a multinucleated Sternberg-Reed giant cell (M.W.) on the right. ($\times 400$)

cells have more regularly shaped, paler-staining nuclei than Sternberg-Reed cells (Miller; Wrong).

In the eczematous lesions and those of generalized exfoliative dermatitis, it is often impossible to make the diagnosis of Hodgkin's disease on histologic grounds because Sternberg-Reed cells frequently are absent. In such instances, the histologic picture is either the same as in mycosis fungoides or shows merely a nonspecific chronic inflammatory infiltrate.

The papular lesions show, as a rule, merely a nonspecific infiltrate of lymphocytes and histiocytes. Occasionally, a few atypical reticulum cells with mitotic figures are present.

7. MYCOSIS FUNGOIDES

Mycosis fungoides affects primarily and predominantly the skin. In the late stage, however, the internal organs may show involvement (Berman; Post and Lincoln).

Several authors (Symmers; Gall and Mallory) have questioned the advisability of regarding mycosis fungoides as an entity. Symmers has called mycosis fungoides a "clinical and pathologic nonexistent," and states that cases reported as mycosis fungoides represent histologically "either Hodgkin's disease, reticulum-cell sarcoma or lymphosarcoma." It is true that some cases which clinically appear as mycosis fungoides prove, on histologic examination, to be one of the other types of lymphoma, and that cases which at the onset show the histologic picture of mycosis fungoides later assume the histologic characteristics of some other form of lymphoma. Nevertheless, mycosis fungoides has a distinct histologic picture which in the majority of cases remains as such throughout the disease and is found also in the internal lesions. Transformation of one form of lymphoma into another occurs not only in mycosis fungoides but also in other forms of lymphoma. This is evidence that all forms of lymphoma are related to each other but it does not obviate any classification.

Clinically, as well as histologically, mycosis fungoides can be divided into three stages, the erythematous ("premycotic" or "pre-fungoid") stage, the plaque stage and the tumor stage. All three stages may be present simultaneously and, occasionally, tumors develop without the previous presence of erythematous or plaque lesions (mycosis fungoides d'emblée) (Eller and Rein).

In the erythematous stage, the eruption may resemble eczema, psoriasis or parapsoriasis or have the appearance of generalized exfoliative dermatitis. Most commonly, one observes scattered, erythematous, scaling patches of irregular outline. They may be poorly demarcated or show a fairly sharp border. Since such lesions often resemble eczema closely, it is always advisable to consider the possibility of early mycosis fungoides when dealing with an atypical, chronic eczematoid eruption. Similarly, in cases of generalized exfoliative dermatitis of unknown genesis, the possibility of mycosis fungoides must always be borne in mind. Itching is a prominent symptom in most instances of early mycosis fungoides.

In the plaque stage, circinate, well-defined, elevated plaques are seen. They may show central clearing, resulting in ringlike lesions.

In the tumor stage, one observes round or lobulated, raised tumors of bluish to brownish red color. They often undergo ulceration.

In rare instances of mycosis fungoides, lesions of poikiloderma

atrophicans vasculare (see page 305) develop either as a precursor or as a residuum of plaque-like lesions.

Histogenesis. The histogenesis of mycosis fungoides is not solved fully. Some authors explain the multiplicity of cell types as due to combined lymphoid and myeloid stimulation (Reimann, Havens and Herbut). A most logical explanation is that first suggested by Fraser (1925, 1936). He regarded mycosis fungoides as a form of reticulum-cell lymphoma and believed that all other cells represented merely a defense reaction of the tissue against the tumor cells. He pointed out that, in the early stage of the disease, the number of tumor cells is small and the inflammatory defense reaction pronounced. As the disease advances, the number of tumor cells increases while the defense reaction slackens, until, finally, in the tumor stage, the tumor cells proliferate uninhibitedly. Fraser's theory finds support in the fact that also in other malignant diseases, such as squamous-cell carcinoma and malignant melanoma, an inflammatory tissue reaction tends to be present as long as the tumor cells are only moderately malignant, but disappears as the malignancy of the tumor cells increases (see "Squamous-Cell Carcinoma," page 330, and "Malignant Melanoma," page 460).

Histopathology. The division of mycosis fungoides into three stages, as described for the clinical picture, pertains also to the histologic picture.

In the first, or erythematous, stage, the histologic picture not infrequently shows merely a banal inflammatory reaction, so that a diagnosis of mycosis fungoides may be impossible. In some instances, however, particularly if several specimens are taken for biopsy and serial sections are made, areas may be found in which specific changes (described in the next paragraph) are present. A finding which should always arouse one's suspicion of mycosis fungoides is the presence of patches of cellular infiltrate deeper in the dermis than one would expect to find them in a banal inflammatory infiltrate. It must be emphasized that the decision whether or not early mycosis fungoides exists often is a very difficult one.

In the second, or plaque, stage, the histologic picture usually is diagnostic. The following six changes may be present: (1) great multiplicity of cell types, (2) polymorphism of the histiocytes, (3) presence of immature and atypical reticulum cells ("mycosis cells"), (4) presence of mitotic figures, (5) presence of a patchy infiltrate in the lower dermis and (6) presence of Pautrier "micro-abscesses."

The variety of cells present includes histiocytes (= mature reticular cells), reticulum cells (= immature reticular cells), lymphocytes, neutrophils, eosinophils, plasma cells and fibroblasts. The number of

eosinophils varies but often is considerable. Histiocytes are numerous. Staining for reticulum with Foot's stain will show, commensurate with the rather large number of histiocytes, a well-developed network of reticulum fibers. The nuclei of the histiocytes vary greatly in size and shape. In addition, their nuclei may show pyknosis (shrinking), karyorrhexis (breaking up into particles, "nuclear dust")

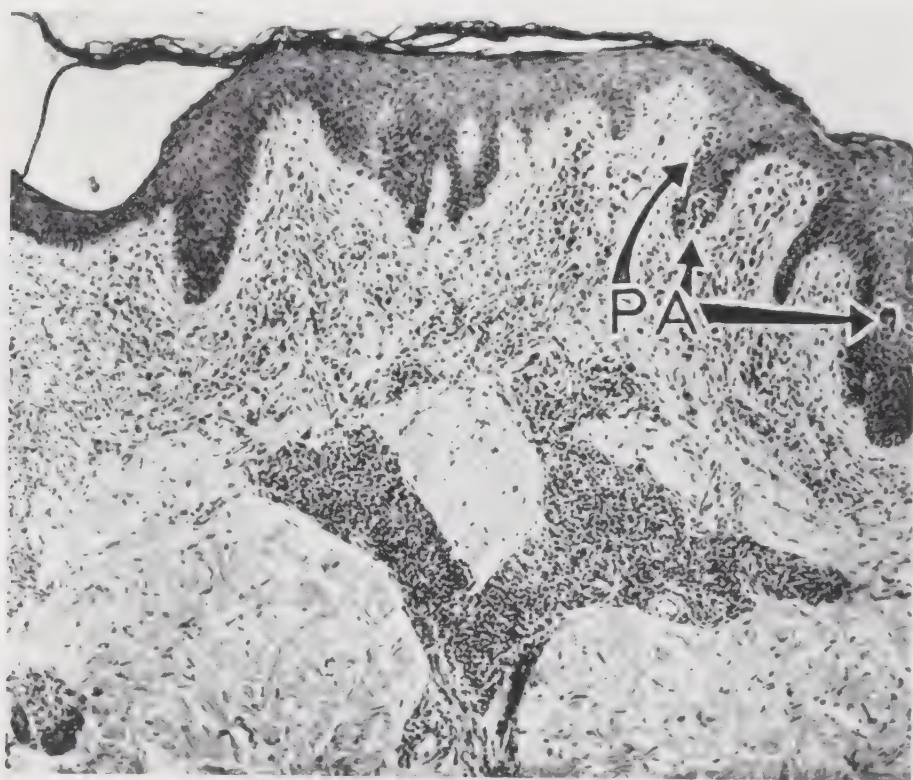


FIG. 268. *Mycosis fungoides*, plaque stage. Low magnification. The infiltrate in the upper dermis is diffuse, while in the lower dermis it consists of variously sized, sharply demarcated patches. The epidermis contains several Pautrier "micro-abscesses" (P.A.). ($\times 100$)

and clumping. Immature and atypical reticulum cells, called mycosis cells, are present. Mycosis cells differ from histiocytes by having larger, more irregularly shaped and more deeply staining nuclei. Mitotic figures, though not numerous, can, as a rule, be found. (An occasional mitotic figure may occur in a banal inflammatory infiltrate, so that the finding of one, two or even three mitotic figures in a section does not necessarily mean mycosis fungoides.) The infiltrate in the plaque stage of mycosis fungoides is located largely in the upper dermis just as in a nonspecific chronic inflammation. Frequently, however, one finds, in addition, patches of cellular infiltrate in the lower dermis (Fig. 268). These patches usually have a blood

vessel in their center. If the patches are fairly large in size, they are strong evidence for lymphoma. An almost pathognomonic finding, occasionally encountered, is the presence of so-called Pautrier "micro-abscesses" in the malpighian layer. They consist of small accumula-

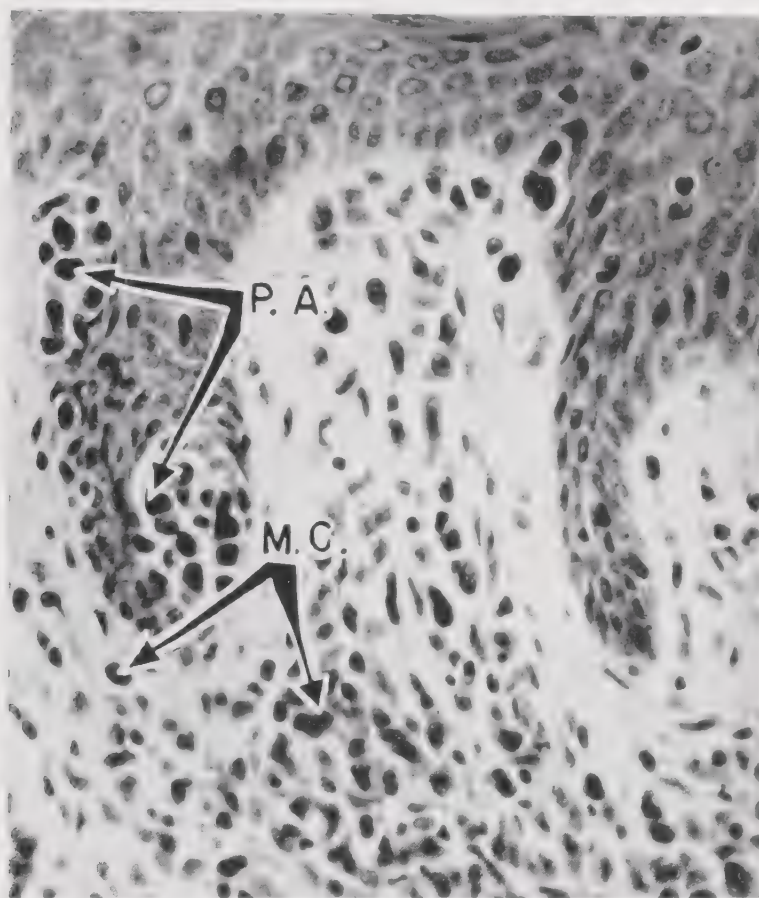


FIG. 269. Mycosis fungoides, plaque stage. High magnification of Figure 268. The infiltrate in the upper dermis shows marked multiplicity of cell types and polymorphism of the histiocytes. Atypical reticulum cells with large, hyperchromatic nuclei ("mycosis cells") are numerous. There are several Pautrier "micro-abscesses" in the epidermis. ($\times 400$)

tions of cells, mainly lymphocytes and histiocytes (Fig. 269). (It should be recalled that the Munro micro-abscesses of psoriasis are located in the horny layer and are composed of neutrophils.) The epidermis in the plaque stage usually shows acanthosis with elongation of the rete ridges and may have an appearance similar to that found in psoriasis.

In the third or tumor stage, the infiltrate consists of large masses of cells and may occupy large areas of the dermis and even penetrate

into the subcutaneous layer. The pressure of the infiltrate may destroy the epidermis so that ulceration results. The infiltrate still shows, as a rule, the same characteristics as in the plaque stage except that the number of mycosis cells and of mitotic figures is larger. In some cases, however, the mycosis cells attain considerable size and may possess more than one nucleus so that they resemble mononu-

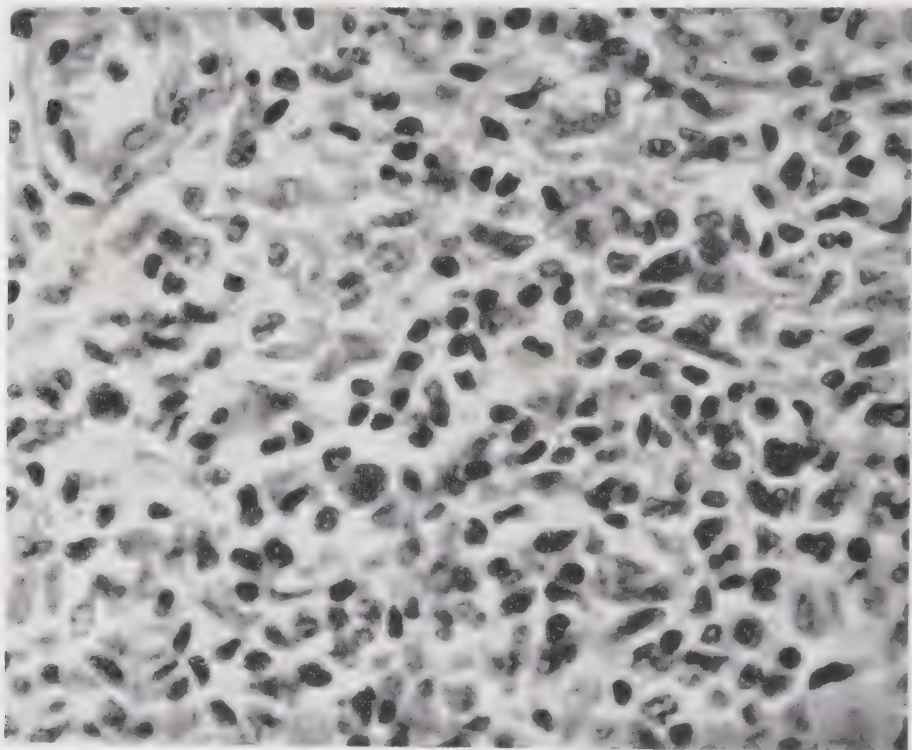


FIG. 270. *Mycosis fungoides*, tumor stage. The infiltrate is polymorphous. There are numerous mycosis cells. Some of them are of considerable size and one, located in the center, has two nuclei. These large mycosis cells resemble mononucleated or multinucleated Sternberg-Reed cells. ($\times 400$)

cleated or multinucleated Sternberg-Reed giant cells (Fig. 270). If such cells are conspicuous, the infiltrate may be identical with that of Hodgkin's disease (Fraser and Schwartz; Wile and Stiles). In other cases, large, immature reticulum cells like those seen in reticulum-cell lymphoma may be present within the multicellular infiltrate (Fig. 271). Occasionally, immature reticulum cells are so numerous and inflammatory cells so few that the infiltrate is identical with that of reticulum-cell lymphoma (Fraser and Schwartz).

The histologic appearance of generalized exfoliative dermatitis in mycosis fungoides may be that of either the erythematous or the plaque stage. If it is that of the erythematous stage, a diagnosis of mycosis fungoides may be impossible (Montgomery).

In poikiloderma atrophicans vasculare due to mycosis fungoides, the epidermis is atrophic and shows vacuolization of the cells of the basal layer. A dense infiltrate lies in the upper dermis in close approximation to the epidermis and invades the epidermis in some areas. The infiltrate may be that of either the erythematous or the plaque stage. As a rule, sufficient atypical cells are present to permit the diagnosis of mycosis fungoides (Oliver; Hazel; Dostrovsky and

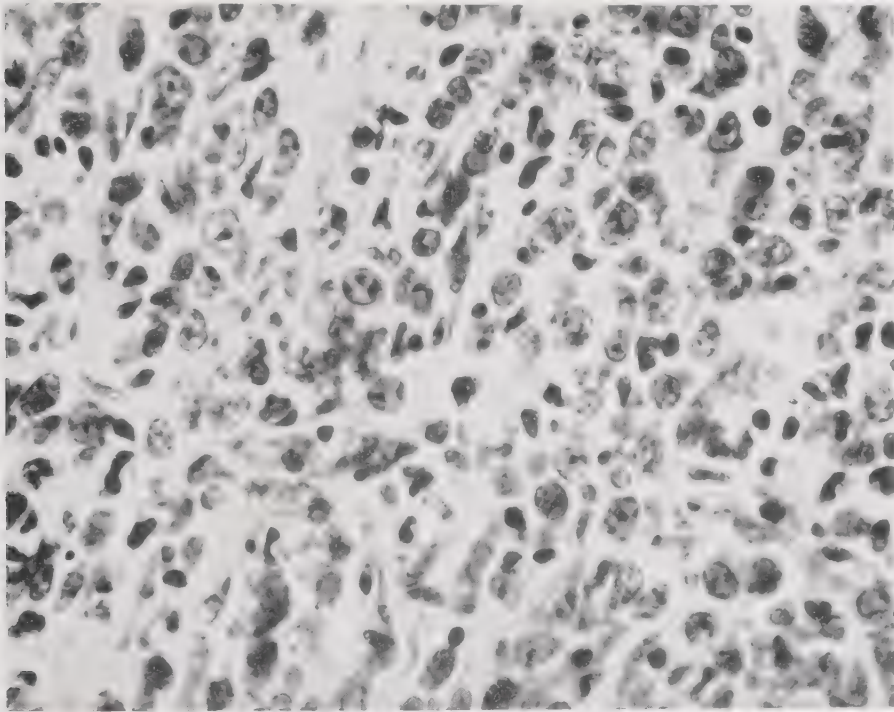


FIG. 271. Mycosis fungoides, tumor stage. The polymorphous infiltrate contains many large, immature reticulum cells like those seen in reticulum-cell lymphoma. ($\times 400$)

Sagher). (For a discussion of poikiloderma atrophicans vasculare, see page 305.)

Involvement of Internal Organs. The incidence of specific visceral lesions in mycosis fungoides is difficult to estimate from the literature. Many reviews set the figure too high, largely because the tendency exists in the dermatologic literature to regard a case of lymphoma as mycosis fungoides just because the primary or predominant lesions of the lymphoma are located on the skin. It should be stressed that, for a diagnosis of mycosis fungoides, it is necessary that the majority of the cutaneous lesions either show, or at least at one time showed, the multiplicity of cell types and the polymorphism of histiocytes characteristic for mycosis fungoides. Heite and Socha, because they included into their series many cases of lymphoma that

were not mycosis fungoides, in a review of autopsies recorded in the literature found visceral involvement in 51 out of 54 cases. Cawley, Curtis and Leach, in their own material, found visceral lesions in 8 out of 10 cases of supposed mycosis fungoides, but only 1 case showed the multiplicity of cell types necessary for a diagnosis of mycosis fungoides and that case had no visceral lesions. It may be estimated that visceral lesions are found on autopsy in only about 20 per cent of the cases of mycosis fungoides; and usually they are not prominent or widespread.

When involvement of the internal organs is present in mycosis fungoides, the infiltrate in the internal organs usually shows the same multiplicity of cell types and polymorphism of the histiocytes as the cutaneous lesions (Ormsby and Finnerud). On the other hand, the visceral lesions, just as some of the cutaneous lesions, may be composed largely of immature reticulum cells and be indistinguishable from reticulum-cell lymphoma (Fraser and Schwartz), or may present, due to the presence of Sternberg-Reed giant cells, the picture of Hodgkin's disease (Fraser; Wile and Stiles; Poulsen).

Of the various internal organs, the subcutaneous lymph nodes are affected most frequently. However, the infiltrate in these lymph nodes is usually not that of mycosis fungoides but is nonspecific inflammatory, showing the histologic characteristics of dermatopathic lymphadenitis (see page 75). Nevertheless, the subcutaneous lymph nodes as well as the internal lymph nodes, the spleen, the lungs, the liver, the kidneys, the gastro-intestinal tract and many other organs may be involved by mycosis fungoides (Berman; Gates; Post and Lincoln). Involvement of the bone marrow, however, has never been reported in true cases of mycosis fungoides (Poulsen). For this reason, mycosis fungoides shows no significant hemocytologic changes except that occasionally immature monocytes or lymphocytes are found in the blood. In rare instances, true lymphatic leukemia develops in the terminal phase of the disease (Lane and Greenwood).

GENERALIZED EXFOLIATIVE DERMATITIS IN LYMPHOMA

Generalized exfoliative dermatitis is a fairly common occurrence in lymphoma. It occurs most commonly in lymphocytic lymphoma, Hodgkin's disease and mycosis fungoides, but also in reticulum-cell lymphoma, particularly when accompanied by monocytic leukemia. Therefore, every case of persistent generalized exfoliative dermatitis requires investigation into the possibility of lymphoma. According to Montgomery, 25 per cent of all cases of generalized exfoliative dermatitis prove to be associated with lymphoma. The histologic picture of generalized exfoliative dermatitis in lymphoma may be,

in the early stage, that of a nonspecific chronic inflammation. In cases in which it is doubtful whether or not lymphoma exists, thorough hemocytologic studies, lymph-node biopsy and sternal marrow biopsy are indicated and additional skin biopsies should be performed at intervals.

HERPES ZOSTER IN LYMPHOMA

The relatively frequent association of herpes zoster, particularly of herpes zoster generalisatus, with lymphoma, is of interest. Herpes zoster is most likely to occur in Hodgkin's disease and in lymphocytic lymphoma, especially when lymphatic leukemia is present.

Histopathology. Histologic examination of the herpes zoster lesions may show the presence of a lymphomatous infiltrate (Barney; Barton and O'Leary). In addition, autopsy may reveal lymphomatous cells in the intercostal nerve, in the spinal ganglion, in the nerve roots or in the cord segment corresponding to the site of the herpes zoster (Bluefarb). It may be assumed that the lymphomatous infiltrate produces a "locus minoris resistentiae" where the zoster virus localizes and multiplies.

LYMPHOCYTOMA CUTIS (LYMPHADENOSIS BENIGNA CUTIS; SPIEGLER-FENDT SARCOID)

This condition occurs in two types: a localized type (Loveman and Fliegelman; Mopper and Rogin) and a disseminated type (Bälverstedt). In the localized type, there is either a solitary nodule or a group of nodules; in the disseminate type, the lesions are scattered widely. The face and the ear lobes are the sites of predilection. The nodules are soft, asymptomatic and radiosensitive. Development into a lymphoma does not seem to occur.

Histopathology. A heavy infiltrate is present in the dermis, usually separated from the epidermis by a narrow zone of normal collagen. The infiltrate occasionally consists only of mature lymphocytes, but, in most cases, there are also reticulum cells. The two types of cells lie either intermingled with one another or in a follicular arrangement. In the latter type of arrangement, lymphocytes surround islands of reticulum cells resulting in structures resembling the follicles of lymph nodes (Fig. 272). The lymphocytes and the reticulum cells are differentiated easily. The lymphocytes have small, round, deeply staining nuclei lying closely packed because lymphocytes possess only little cytoplasm. The reticulum cells have large, irregularly shaped, pale nuclei lying in loose arrangement because these cells possess ample amounts of cytoplasm separating the nuclei from one another (Fig. 273). Mitotic figures are usually present, though in small numbers.

The nature of lymphocytoma cutis is not known. Although it suggests a lymphoma in its histologic architecture and is highly radio-sensitive, it apparently is not a form of lymphoma. European authors (Hallam and Vickers; Hellier; Bälverstedt) have suggested that it represents a hyperplasia of pre-existing rudimentary lymphoid tissue.

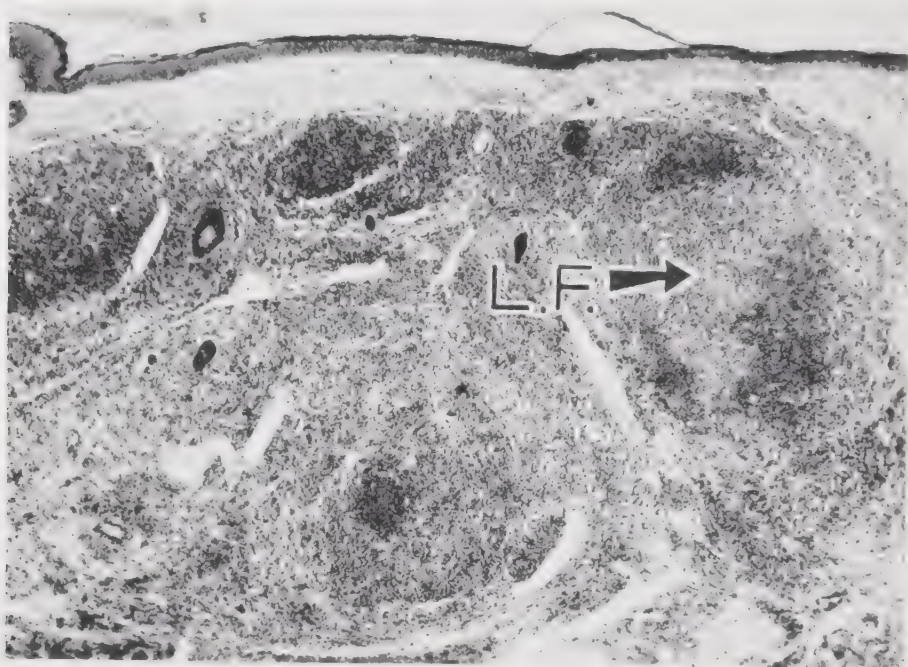


FIG. 272. Lymphocytoma cutis (lymphadenosis benigna cutis, Spiegler-Fendt sarcoid). Low magnification. The infiltrate is composed of two types of cells: lymphocytes, which lie in the dark-staining areas, and reticulum cells, which lie in the light-staining areas. At the right (L.F.), the arrangement of these cells resembles that encountered in a lymph follicle. ($\times 50$)

Differential Diagnosis. The diagnosis is easily established in those cases of lymphocytoma cutis in which the infiltrate shows lymphocytes and reticulum cells in follicular arrangement. Even in cases in which the two cell types lie intermingled, the diagnosis usually can be made because the cells composing lymphocytoma, in contrast with those of reticulum-cell lymphoma, are mature. Nevertheless, mistakes in diagnosis occur (Director and Kern). The greatest difficulties in diagnosis occur in those cases with a purely lymphocytic infiltrate because it may be impossible to rule out lymphocytic lymphoma. It is thus advisable always to make a diagnosis of lymphocytoma cutis with reservations, except in cases with obvious follicular formations (Loveman and Fliegelman).

Differentiation from follicular lymphoma (Brill-Symmers disease), with which lymphocytoma cutis is not related, is not difficult since in follicular lymphoma the follicular centers are larger, more numerous and outlined more distinctly. Also, they are partially separated from the surrounding stroma by fissures which probably are the result of shrinkage of tissue during fixation. Such fissures are not apt to occur in lymphocytoma cutis.

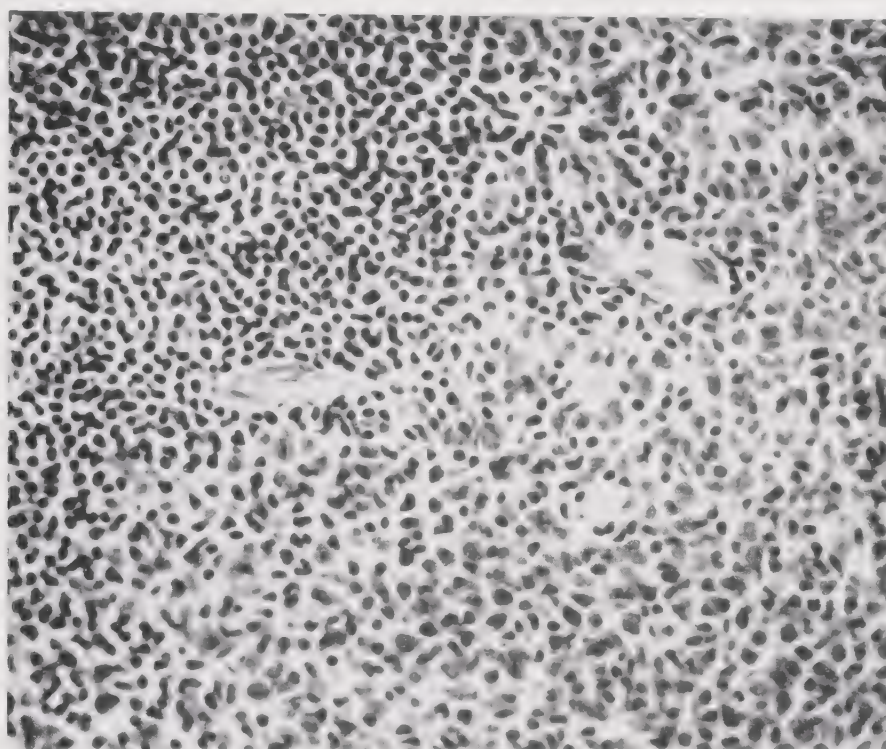


FIG. 273. Lymphocytoma cutis (lymphadenosis benigna cutis, Spiegler-Fendt sarcoid). High magnification of Figure 272. Lymphocytes lie in the left upper half, reticulum cells in the right lower half of the illustration. ($\times 200$)

MYELOSIS

Myelosis is nearly always associated with leukemia, in contrast with lymphoma, in which leukemia is often absent. The type of leukemia is myeloid leukemia. On the other hand, cutaneous lesions are less common in myelosis than in lymphoma. Specific and nonspecific cutaneous lesions may occur, however. Just as in lymphoma, there is no clearcut distinction between the two. The two conditions merge imperceptibly and it is probable that most if not all of the nonspecific cutaneous manifestations result from tumor cells (Gates) (see page 472).

Clinically, the specific cutaneous lesions consist of from pinhead- to walnut-sized, firm nodules, which may coalesce into plaques and occasionally ulcerate. The nonspecific cutaneous lesions (leukemids) may consist of macules, papules, pustules and purpuric lesions.

Histopathology. Histologic examination of specific lesions shows the presence of dense masses of cells in the dermis and, occasionally, in the subcutaneous layer. Frequently, rows of cells extend from these masses into the surrounding tissue. In addition, small groups of cells may be found scattered in the tissue spaces. The majority of cells belong to the myeloid series, but lymphocytes and phagocytic histiocytes not infrequently are observed (Ketron and Gay). Some of the cells of the myeloid series are mature, but most are immature, being either myeloblasts or myelocytes. They may be so immature that it is impossible to decide whether they belong to the myeloid or to the lymphoid-reticular series of cells.

Myeloblasts are about double the size of a mature polymorphonuclear leukocyte. They possess a large, oval or round, pale-staining nucleus and relatively little, nongranular cytoplasm. They resemble lymphoblasts, although, as a rule, lymphoblasts have a coarser chromatin structure and less cytoplasm (Nekam). Myelocytes are about the same size as myeloblasts or slightly smaller. They have, however, a smaller, indented or lobate nucleus and abundant cytoplasm, containing granules which may be either fine neutrophilic or coarse eosinophilic. Myeloblasts may or may not give a positive peroxidase reaction (also called oxidase reaction), while myelocytes always give a positive peroxidase reaction.

The peroxidase reaction indicates the presence of the enzyme peroxidase, which occurs in mature and partly matured cells of the myeloid series but is absent in very immature cells of the myeloid series and in all cells of the lymphoid-reticular series. The peroxidase reaction is of great diagnostic value since it is positive in the majority of cases with myelosis and always negative in lymphoma. Even very immature tumors of myelosis usually show at least a few areas in which the reaction is positive. For the peroxidase reaction, the specimen should be fixed in a 10 per cent formalin solution. Frozen sections are used for staining. On staining, peroxidase-positive cells show numerous black granules (Ketron and Gay).

Occasionally, the myeloid cells found in the cutaneous lesions are more immature than those in the bone marrow and the circulating blood. This may be regarded as evidence that the cutaneous lesions in myelosis are autochthonous (Paul and Limarzi). It is probable that the myeloid cells form by myeloid transmutation of local reticular cells (Heller, Lewisohn and Palin).

CHLOROMA represents a rare form of myelosis in which the myeloblasts and the myelocytes show an unusual tendency to tumor formation. The tumors are found most commonly in the bones, especially the flat bones, but may occur also in the skin. The peroxidase reaction is usually positive in the tumors. The nature of the green pigment present in the tumors is not yet fully known. It represents an intermediary product in the breakdown of hemoglobin to bilirubin (Goodman and Iverson).

"MONOCYTIC LEUKEMIA OF THE NAEGLI TYPE" is a form of myeloid leukemia, in contrast with monocytic leukemia of the Schilling type, which is true monocytic leukemia. In the Naegeli type, the infiltrate in the cutaneous lesions is composed mainly of monocyte-like cells, so that differentiation from true (Schilling's) monocytic leukemia is not possible. In the blood, however, myeloblasts and myelocytes are present, in addition to monocyte-like cells, and the bone marrow shows myeloblastic hyperplasia without changes in the reticular cells (Watkins and Hall). While some regard monocytic leukemia of the Naegeli type as myeloid leukemia with a predominance of monocytes, most authors believe that the monocyte-like cells differentiate from myeloblasts. Montgomery and Watkins favor the latter view, since they observed cells intermediate between myeloblasts and the monocyte-like cells.

EOSINOPHILIC LEUKEMIA, a rare form of myeloid leukemia, occasionally has cutaneous lesions. The cellular infiltrate present in the dermis may consist largely of immature, primitive cells with but a few myelocytes and no eosinophils (Carmel, Minno and Cook), or it may contain numerous eosinophils (Deme).

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Glossary

Acantholysis: Loss of coherence between epidermal cells due to degeneration of the intercellular bridges. It leads to the formation of clefts, vesicles and bullae within the epidermis. Occurs in pemphigus, Darier's disease, familial benign chronic pemphigus, virus bullae and senile keratosis.

Acanthosis: Increase in thickness of the stratum malpighii.

Altération cavitaire: See "Intracellular Edema."

Anaplasia: Atypical de-differentiation of cells occurring in malignant diseases. Anaplastic cells have large, hyperchromatic, irregularly shaped nuclei and frequently show atypical mitotic figures.

Ballooning degeneration: A type of degeneration of epidermal cells causing marked swelling with loss of the intercellular bridges. Acantholysis results and a bulla forms. Ballooning degeneration occurs in virus vesicles and is diagnostic of them. See also "Reticular Degeneration of Epidermal Cells."

Bulla: A cavity forming either within or beneath the epidermis and filled with lymph fluid. A small bulla generally is called a vesicle; and a slitlike bulla, as seen in Darier's disease and senile keratosis, a lacuna. About the different modes of formation of bullae, see the introduction to Chapter 7.

Caseation necrosis: A type of tissue death in which the affected area has lost its structural outline and consists of pale eosinophilic, amorphous, finely granular material. Unless the necrosis is far advanced, some pyknotic nuclei are still present. No invasion of neutrophils occurs. Caseation necrosis occurs especially in tuberculosis, syphilis, granuloma annulare and beryllium granuloma.

Dyskeratosis: Faulty keratinization of individual epidermal cells. There are two types, one occurring in benign diseases and the other in malignant diseases. "Benign" dyskeratosis occurs in Darier's disease and, occasionally, in familial benign chronic pemphigus, and consists of the formation of corps ronds and grains (see page 49). "Malignant" dyskeratosis occurs especially in Bowen's disease but also in squamous-cell carcinoma and senile keratosis and consists of premature and atypical keratinization of individual cells.

Hydropic degeneration of basal cells: See "Liquefaction Degeneration of Basal Cells."

Hyperkeratosis: Excessive thickness of the horny layer. If caused by excessive formation of keratin, the granular layer is also thickened, as in lichen planus and lupus erythematosus. If caused by retention of the horny layer, as in ichthyosis vulgaris, the granular layer is even smaller than normal.

Incontinence of pigment: Loss of melanin from the cells of the basal layer due to damage to these cells with accumulation of the melanin in the upper dermis, inside as well as outside of melanophores. It occurs in an idiopathic form: in the disease called incontinentia pigmenti; and in a symptomatic form: in lichen planus, lupus erythematosus, poikiloderma atrophicum vasculare, Riehl's melanosis and melanodermatitis toxica.

Intercellular edema (spongiosis): Edema between squamous cells causing an increase in the width of the spaces separating them. It occurs frequently in inflammatory processes of the skin, especially in dermatitis-eczema. It does not cause formation of bullae or vesicles but contributes to their increase in size. See also "Intracellular Edema."

Intracellular edema (altération cavitaire): Edema within squamous cells. If severe, it results in reticular degeneration (see below) of the affected cells and in the formation of multilocular bullae.

Karyorrhexis: Fragmentation of nuclei.

Liquefaction degeneration of basal cells: A type of degeneration causing vacuolization and disintegration of basal cells. It occurs in incontinentia pigmenti, lichen planus, lupus erythematosus, poikiloderma atrophicum vasculare, Riehl's melanosis, melanodermatitis toxica and lichen sclerosus et atrophicus with its variants kraurosis vulvae and balanitis xerotica obliterans. In several of these diseases, the liquefaction degeneration may cause incontinentia pigmenti (see above). In lichen planus, lupus erythematosus and lichen sclerosus et atrophicus, it may cause the formation of subepidermal bullae (see under "Formation of Bullae," introduction to Chapter 7).

Metachromasia: The phenomenon of reacting with a different color than that of the dye used for the staining. Important examples of metachromasia occur in the staining of the granules of mast cells (see "Urticaria Pigmentosa"), and in the staining of mucin (see "Myxedema"), of amyloid (see "Amyloidosis") and of the fibrinoid material in fibrinoid degeneration (see "Acute Systemic Lupus Erythematosus"). All four materials

stain purple with toluidine blue, methylene blue, thionine and cresyl violet. Incidentally, all four materials, because of the presence of polysaccharides, stain deeply red with the periodic acid-Schiff reaction.

Metaplasia: Change of one type of tissue into another, as it occurs, for instance, in the formation of bone in scars and in calcifying epithelioma (see "Osteoma").

Micro-abscesses: Small accumulations of cells in the epidermis. Two types of micro-abscesses occur: the micro-abscess of Munro in psoriasis and the micro-abscess of Pautrier in mycosis fungoides. For their description, see those two diseases.

Papilloma: A tumor or tumor-like proliferation of the skin characterized by papillomatosis (see below) and hyperkeratosis. Five diseases show this type of proliferation: nevus verrucosus (Jadassohn), keratosis senilis, basal-cell papilloma, verruca vulgaris and acanthosis nigricans. In typical instances, histologic differentiation of these five diseases is easy, but occasionally no more specific diagnosis than papilloma can be made.

Papillomatosis: Upward proliferation of papillae causing the surface of the epidermis to show irregular undulation.

Parakeratosis: Imperfect keratinization resulting in the retention of nuclei in the horny layer of the epidermis. The granular layer is absent in areas of parakeratosis.

Pyknosis: Shrinking of nuclei.

Reticular degeneration of epidermal cells: A process in which severe intracellular edema causes bursting of epidermal cells and formation of a multilocular bulla. The septa inside the bulla are formed by resisting cell walls. Reticular degeneration plays a role in the formation of virus vesicles and those of contact dermatitis.

Spongiform pustule of Kogoj: A multilocular pustule located in the upper stratum malpighii and characterized by the presence of neutrophils inside of edematous epidermal cells. The cellular walls of these epidermal cells traverse the pustule like the network of a sponge. This type of pustule has a diagnostic appearance and occurs in acrodermatitis continua of Hallopeau, impetigo herpetiformis, keratosis blennorrhagica and Reiter's disease.

Spongiosis: See "Intercellular Edema."

Vesicle: A small bulla (see "Bulla"). No sharp borderline can be drawn between a vesicle and a bulla. Generally, the term bulla is preferred in histopathology except for very small lesions that clinically are hardly visible.

Villi: Elongated and often tortuous papillae which are covered, as a rule, with but one or two layers of epidermal cells and extend into a vesicle, a bulla or a cystic cavity. Formation of villi is observed in Darier's disease, familial benign chronic pemphigus, pemphigus vulgaris, pemphigus vegetans, syringocystadenoma papilliferum and hidradenoma papilliferum.

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